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THE UNIVERSITY OF ALBERTA
PREPARATION AND PROPERTIES OF 2-NITROGLYCALS

BY
IAN K. O'NEILL

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF ALBERTA
EDMONTON, ALBERTA

OCTOBER, 1966

UNIVERSITY OF ALBERTA
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read, and
recommend to the Faculty of Graduate Studies for acceptance,
a thesis entitled,

PREPARATION AND PROPERTIES OF 2-NITROGLYCALS
submitted by Ian K. O'Neill, in partial fulfilment of the
requirements for the degree of Doctor of Philosophy.

ACKNOWLEDGEMENTS

The author expresses his gratitude for the guidance and valuable advice received from Professor R. U. Lemieux during the course of this work.

Special thanks are due to the technical staff of the Department of Chemistry for the co-operation received and to Mrs. S. Fraga for collaboration in the preparation of acetylated glycals.

The patient secretarial assistance provided by the author's wife, Jean, and Miss Marleen Jackson, is gratefully acknowledged, as is the proof-reading performed by Drs. Gunner, Watanabe and White.

The author greatly appreciated many enjoyable discussions with his associates.

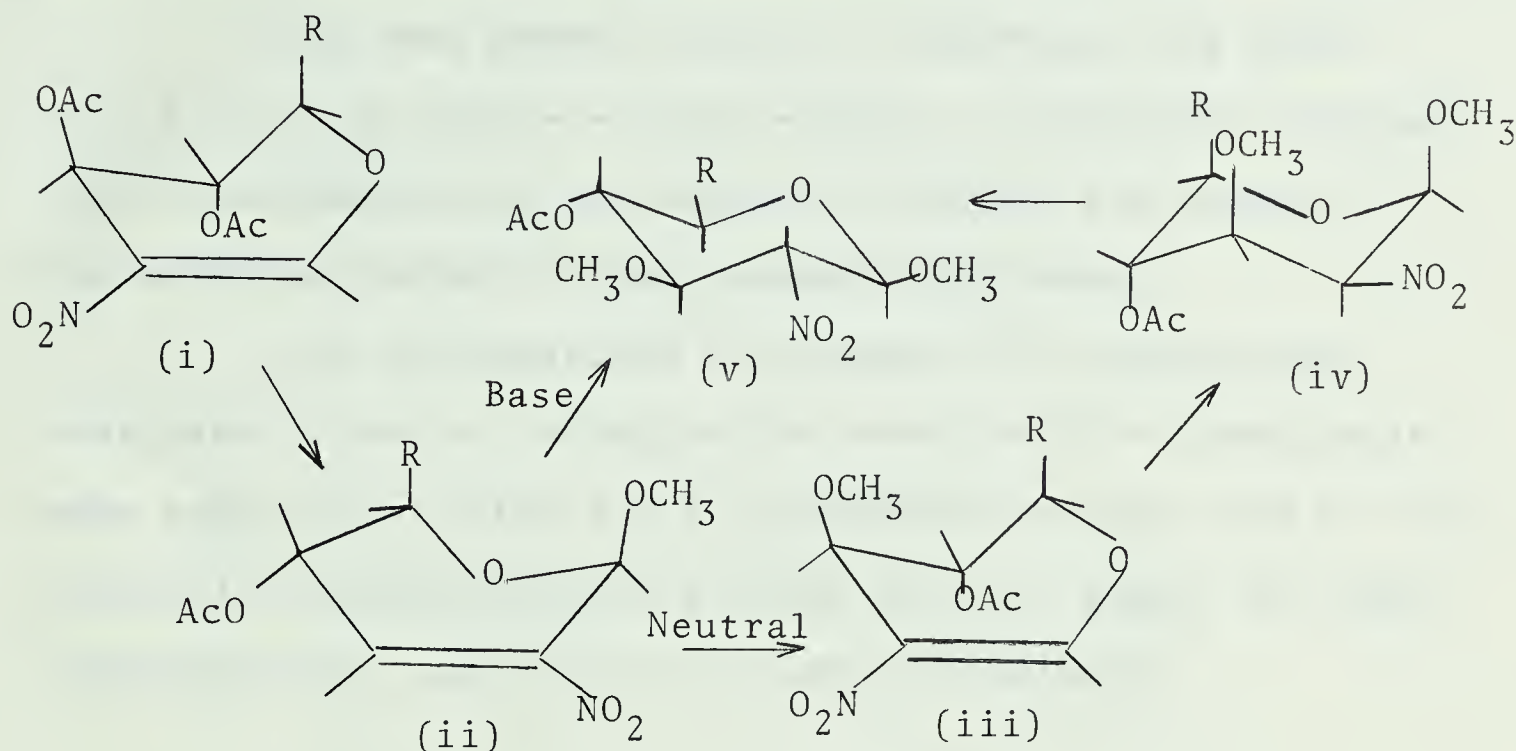
ABSTRACT

The initial purpose of this work was the preparation of α -glycosaminides since many biologically active compounds contain this residue. Previous syntheses have been based upon the reaction of aminosugars but good yields of the α -anomer are only obtained with the simple alcohols. These are often of limited value since most aminosugars themselves require multi-step syntheses. A new approach lay in the establishment of the glycosidic linkage prior to introduction of the amino function. Accordingly, various nitrogenous electrophilic reagents were reacted with acetylated 1,2-unsaturated sugars (acetylated glycols). Nitrosyl chloride and dinitrogen tetroxide provided high yields of the corresponding acetylated cis-2-deoxy-2-nitroso- α -glycopyranosyl chlorides and acetylated 2-nitroglycols, respectively. This thesis is concerned mainly with this reaction of dinitrogen tetroxide and the properties of the acetylated 2-nitroglycols, which are a hitherto unknown group of compounds.

The reaction of dinitrogen tetroxide was found to be markedly dependent upon solvent and temperature and, in other conditions, provided good yields of unstable acetylated cis-2-deoxy-2-nitroso- α -glycopyranosyl nitrates which had similar properties to those of the acetylated cis-2-deoxy-2-nitroso- α -glycopyranosyl chlorides.

The acetylated 2-nitroglycols (i) were treated with methanol and found to give complex sequences of reactions leading eventually to compounds of type (v) In the case of 3,4-

di-O-acetyl-2-nitro-D-xylal (i, R = H), the 2,3-unsaturated methyl glycoside (ii) was observed as an intermediate both



under neutral and basic conditions. Base catalysis was required to obtain a high yield of (v) in a convenient time. In the absence of base, two additional intermediates (xii) and (iv) were observed. It was shown that (iii) is not an intermediate in the presence of base. All the steps were found to be highly stereospecific and it is possible to rationalise this feature through a consideration of the steric requirements of the nitroolefin portion of the nitroglycals. The strong $A^{(1,2)}$ interaction which would be relieved with a quasi-axial group at the 1- and/or 3-positions leads, for example, to conformations approximating those indicated in formulas (i), (ii) and (iii). The reactions undoubtedly proceeded by way of aci-salt intermediates which, however, could not be observed. The aci-nitro group of these intermediates will

have an $A^{(1,3)}$ interaction with neighboring groups and this also influences the stereochemical route of reaction.

The same general series of reactions was given by 3,4,6-tri-O-acetyl-2-nitro-D-glucal ($i, R=CH_2OAc$) although the stereospecificity was reduced, probably for reasons of the anchoring effect of the acetoxymethyl group.

The conformations of a number of 2-substituted acetylated glycols, including the acetylated 2-nitroglycols, were established using P.M.R. parameters derived from the 3-O-acetyl-4,6-O-benzylidene-D-glycols with the gluco- and allo-configurations, and from tri-O-acetyl-D-galactal.

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LIST OF COMPOUNDS DESIGNATED

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INTRODUCTION

a) The Purpose of the Present Work

2-Amino-2-deoxysugars are widespread in nature (1,2,3) and are often found in important pharmaceutical and biological compounds, e.g. streptomycin, paromomycin (3), trehalosamine (4) and teichoic acids (5). These examples, together with many others, contain α -glucopyranosaminide residues.

Difficulties have been encountered in the formation of the glycosidic linkage with the 2-amino-2-deoxysugars, particularly the α -linkage. Thus, alcoholysis of 2-acetamido-2-deoxy-D-glucose in the presence of acid (6), a procedure which provides the best yields of the α -glycosaminides is limited to those situations where the alcohol can be used as solvent. The α -glycosaminidic linkage has been made with more complex alcohols such as other sugars (5,7) by making use of the Koenigs-Knorr type reaction. This procedure involves reaction of the protected 2-amino-2-deoxy- α -D-glucopyranosyl halide with the alcohol in the presence of silver or mercuric salts, and inherently provides low yields of the corresponding α -glycosides.

Additional problems arise from the multi-step syntheses required in the preparation of some aminosugars. Thus, although D-glucosamine is

readily available from chitin, D-mannosamine (8) and D-galactosamine (9) have only been prepared in low overall yields. Therefore, new routes for the syntheses of aminosugars and their glycosides were investigated in the present work. The syntheses of aminosugars has recently been reviewed (10).

b) 2-Deoxy-2-nitrososugars and 2-Nitrosugars

A possible route to a α -glycosaminides was through the establishment of the glycosidic linkage prior to placing the amino function at the 2-position. It was thought that nitrosyl chloride would react readily with 1,2-unsaturated sugars to yield 2-deoxy-2-nitrosoglycosyl chlorides. The reactions of nitrosyl chloride with alkenes (11) and of 1,2-unsaturated sugars with electrophilic reagents (12) supported this hypothesis.

Thus tri-O-acetyl-1,2-dideoxy-D-arabino-hex-1-enopyranose (tri-O-acetyl-D-glucal)*, tri-O-acetyl-1,2-dideoxy-D-lyxo-hex-1-enopyranose (tri-O-acetyl-D-galactal)*, and di-O-acetyl-1,2-dideoxy-D-threo-pent-1-enopyranose (di-O-acetyl-D-xylal)*, were found in joint investigation with T. L. Nagabhushan (10,13) to provide near quantitative yields of the corresponding dimeric acetylated 2-deoxy-2-nitroso- α -D-aldopyranosyl chlorides. These cis additions were not altogether surprising since similar cis additions by chlorine

*

Henceforth the more convenient trivial glycal nomenclature will be used exclusively.

to these systems had previously been observed (14), and during the course of this work, Meinwald et al. (15) reported the cis addition of nitrosyl chloride to norbornene. Concurrent with this work, a report (16) appeared of addition by nitrosyl chloride to acetylated D-glucal and D-arabinal.

These dimeric addition compounds were found to be unstable, decomposing to the corresponding acetylated 2-nitroglycals, members of a hitherto unknown class of compounds. The preparation of these compounds was investigated accordingly and form the main subject of this thesis. It was found that they were readily prepared in high yield by reaction of the acetylated glycals with dinitrogen tetroxide in methylene chloride at -80° . Other conditions led to formation of nitrosonitrate adducts.

c) The Structure of Dinitrogen Tetroxide and Its Reactions with Alkenes

Several extensive surveys of the literature have been made (17-20) and varying conclusions drawn from many differing (and sometimes conflicting) results. Eight types of addition products have been observed, (see over) (19).

That some products resulted through the use of impure dinitrogen tetroxide and the oxidation of the initial products was shown by Levy, Scaife and co-workers (21). Admixing oxygen with the dinitrogen tetroxide eliminated the dinitrogen

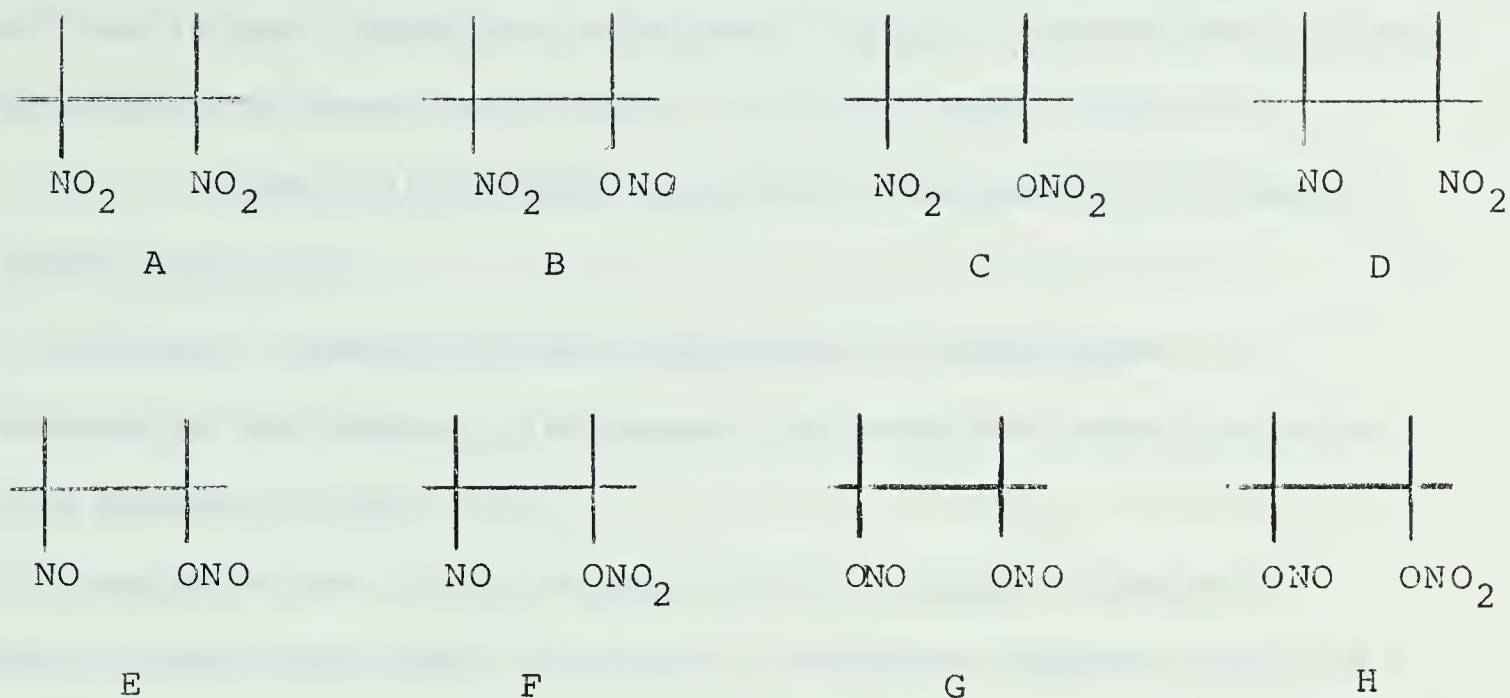


FIG. 1. Previously observed products of addition of dinitrogen tetroxide to alkenes.

trioxide present and thus the addition products, D and E. Oxidation of initial products was minimized by limiting the quantities of oxygen and dinitrogen tetroxide used, thus minimizing the formation of C. It was assumed that C was produced from the oxidation of B, although it may have also been produced by oxidation of F. No recent report of G or H has been made and quite possibly these products never existed. Several reports (e.g., 22 and 23) of the nitrosonitrates, F, can be found, each time having been prepared in ethereal solvents. The early reports of the preparation of such compounds were usually disputed.

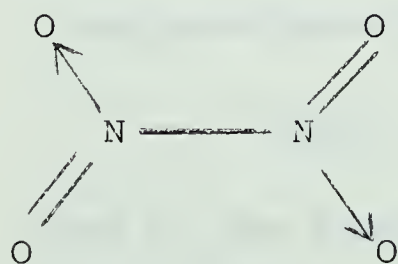
Free-radical reactions have been observed (18) and both conjugated and non-conjugated nitroalkenes have

resulted. Nitroalkenes may have arisen through decomposition of the initial addition products. In this connection, nitro-nitrites (B) have been found (21) to be very unstable.

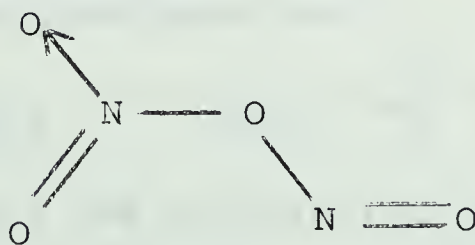
Alkene-dinitrogen tetroxide reactions are greatly influenced by:

- i) solvent - many solvents complex with dinitrogen tetroxide and thereby influence the relative stabilities of the isomeric forms (19),
- ii) temperature - the proportion of nitrogen dioxide to dinitrogen tetroxide is greater at higher temperatures and therefore, moderation of the reaction mixture temperature is an important factor (21),
- iii) alkene - the relative rates of formation and stabilities of the various products are greatly influenced by electron-withdrawing substituents (24).

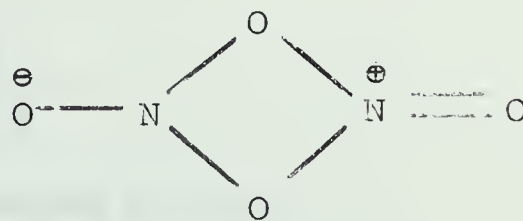
The structure of dinitrogen tetroxide in relation to its reactions has been reviewed (25). X-ray diffraction measurements (26,27) have shown that crystalline dinitrogen tetroxide has the dinitro form, J, with a very long N-N bond (1.72Å). This N-N bond has been shown (28) to have a strength of the order of 13 kcal/mole.



J



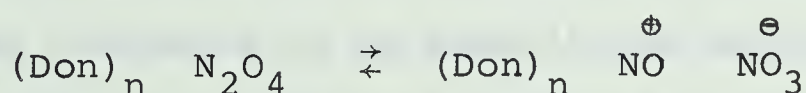
K



L

On the basis of the adjacent charge rule, Pauling and Brockway (29) suggested the nitrosylnitrate structure, (K). Longuet-Higgins (30) has also suggested the structure L. Studies of dinitrogen tetroxide in the liquid and gaseous phases have shown no evidence that only one structural isomer exists under these conditions. Assumptions were made (31) in assigning structure J from the results of an electron diffraction study of the gas. The I.R. and Raman spectra of gaseous and liquid dinitrogen tetroxide (32) seemed to favour J, to definitely exclude K, but not L. Recently (33), however, gaseous dinitrogen tetroxide has been trapped in argon and oxygen matrices at liquid helium temperature and examined by I.R. spectroscopy. The spectra showed the presence of J and K and also one unidentified isomer. Dipole moment studies (e.g. 34) of dinitrogen tetroxide have shown that the molecule cannot have a structure which is both symmetrical and planar since the dipole moment is greater than that of nitrogen dioxide itself. However, it has been suggested (35) that serious errors arise in the calculation of the dipole moment.

Dinitrogen tetroxide forms complexes (36) with many compounds which can function as 'onium- or π -donors. These complexes have been formulated as



and it was found that the equilibrium depended on the donating power of the donor. Thus, amines give the most

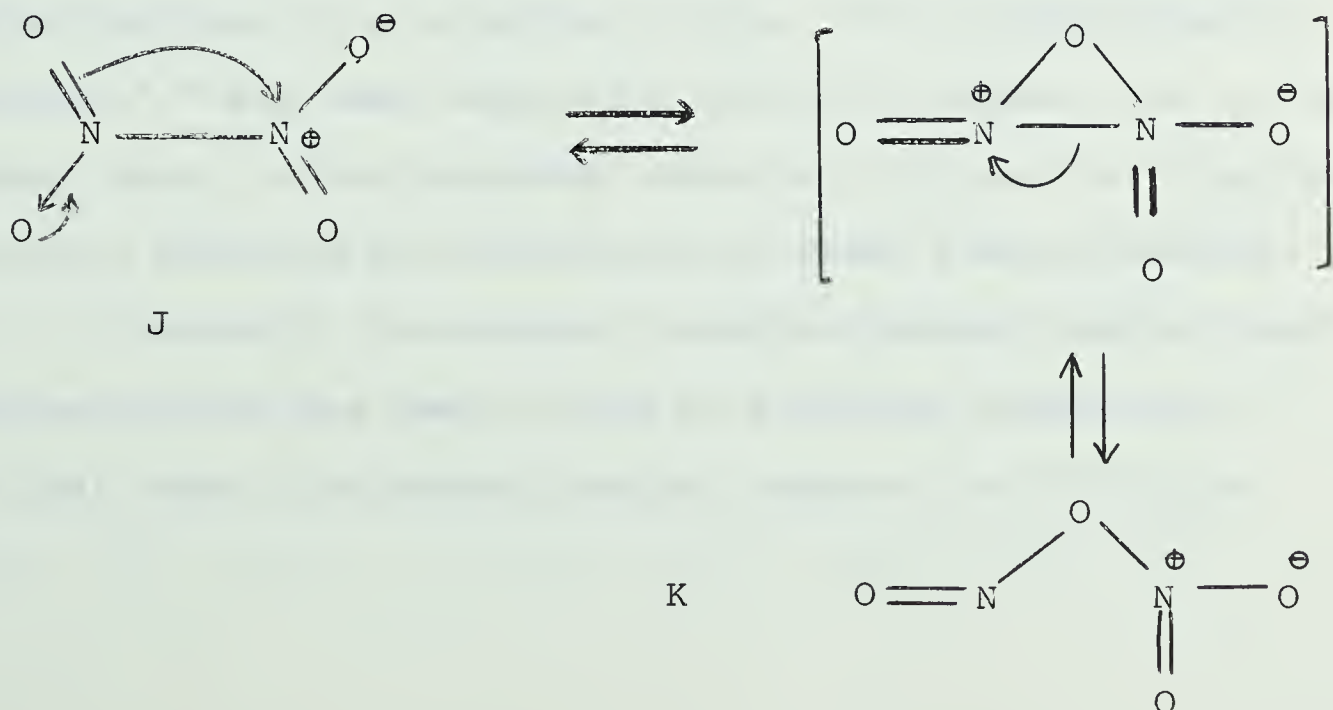
ionic complexes. Usually, however, the equilibrium lies far to the left, as was shown by U.V. absorption measurements (37).

Neat, liquid dinitrogen tetroxide contains little of the ionic nitrosyl nitrate, but some is definitely present. $(\text{C}_2\text{H}_5)_4\text{N}^+ {}^{15}\text{NO}_3^-$ dissolved in dinitrogen tetroxide underwent complete isotopic exchange with the solvent (38).

Chemically dinitrogen tetroxide exhibits the properties of nitrosyl nitrate (25), for example, in its reactions with metals (39) and strong acids (40). Free-radical reactions, e.g. vapour phase nitration, are usually associated with the monomeric form. Certainly, the compound does not always react as nitrosyl nitrate. An interesting paper by White and Feldman (41) demonstrated great selectivity in dinitrogen tetroxide substitution reactions which have a bearing on glycol-dinitrogen tetroxide addition reactions examined in the present research. They observed that the reaction with alcohols and secondary amines gave nitrites and nitrosoamines at 0° with ether as solvent. However, use of lower temperatures (-80°) and methylene chloride as solvent, changed the course of the reactions to produce nitrate and nitramines, respectively.

Schaarschmidt (42) suggested in 1925 that dinitrogen tetroxide is an equilibrium mixture of structural isomers, but only recently has this hypothesis been invoked to explain the varying results. A hypothesis that invokes

both preferential solvation of structural isomer K and a change in the equilibrium position with temperature does accommodate all results obtained so far. Thus dinitrogen tetroxide in nitric acid exists almost completely as the ionic nitrosylnitrate form (K) (43). However, the I.R. measurements mentioned previously (33) have indicated that at very low temperatures structural isomer J is the most stable form and, since X-ray measurements (26,27) upon the crystalline form showed J to be the isomer present in the solid, it may be concluded that J is the most thermodynamically favored isomer under these conditions. In view of this evidence, an equilibrium must exist. Most authors write equilibration proceeding through the monomeric form, but whether such a process is really necessary is open to question. For example, a change of the dinitro form (J) to the nitrosylnitrate form (K) could conceivably proceed by way of the rearrangement depicted below involving heterolytic processes.



d) The P.M.R. Spectra and Conformations of
Acetylated Glycals

The P.M.R. parameters of a considerable number of 2,3-unsaturated sugars have been published (see DISCUSSION, section 1), but of the 1,2-unsaturated sugars only the complete set of parameters of tri-O-acetyl-D-glucal (44) has so far appeared. The acetylated 2-nitroglycals had unexpected coupling constants and this led to a P.M.R. spectroscopic examination of a number of available glycals. Relationships between the dihedral angle and the coupling constants were developed for several situations.

Since the first use of P.M.R. parameters for configurational assignments (45), the general expression,

$$J = x \cos^2 \theta + y \quad (46)$$

has found general acceptance. The term "y" allows for some π contribution to the coupling, but is usually negligible for vicinal protons in a saturated system. The proportionality constant "x" has been assigned a number of values, and in the present work, it was assigned values on the basis of coupling constants observed for situations of fixed stereochemistry.

Recently, the vicinal coupling between olefinic and allylic protons has been fitted to a similar expression (47, 48) where the proportionality constant is ~ 11 c.p.s.

In the case of long-range allylic coupling (over four bonds including the double bond), Garbisch (49) has proposed

$$J = 1.3 \cos^2 \theta - 2.6 \sin^2 \theta \quad (0^\circ \leq \theta \leq 90^\circ).$$

Examination of examples cited by the latter author, and those by Sternhell (50) and Barfield (51) indicate that a relationship of this type which accounts for both σ and π coupling, is necessary.

Conformational analysis of the glycal series was considerably hampered by the lack of similar analyses for other dihydropyran systems. However, the cyclohexene ring has been studied previously by several workers (48, 52 - 58) and analogies can be drawn between the two systems. In general there appear to be three conformation - determining factors, i) the "para" distance (59), ii) the so-called $A^{(1,2)}$ interaction (60), and iii) other interactions.

The first factor should not operate here since 1,4-dioxene, with an even shorter "para" distance than the dihydropyran systems, has been shown (61) to essentially adopt the half-chair form. The other two factors are dependent upon the substituents on the ring.

In such conformational analyses, based on P.M.R. parameters, great care must be taken not to interpret the available data too deeply. In carbohydrate conformational analysis, ring flattening (62 - 65) has not usually been taken into account, although machine computations (66)

have shown that such a process, which involves increasing the angles within the ring (65), requires little expenditure of energy. The observed splittings in the P.M.R. spectra, besides the possibility of not being correctly interpreted on a first order basis, are also subject to electronegativity and other effects (67).

e) Nitrosugars - Their Preparation and Properties

The general method of preparation has involved the condensation of nitroalkenes, usually nitromethane, with aldehyde(s) in the presence of base. This reaction, which is analogous to the aldol condensation, was discovered by Henry (68). It has been used in chain-lengthening procedures (69) and in the preparation (70) of 2-deoxy-2-aminosugars. The condensation (71) with the "sugar dialdehydes" formed from periodate oxidation of glycosides to yield 3-deoxy-3-nitrosugars is similar to the condensation (72) with five-carbon sugar dialdehydes to yield six-carbon deoxynitroinositols, and to the base-catalysed conversion of 6-deoxy-6-nitroglycosides to deoxynitroinositols (73).

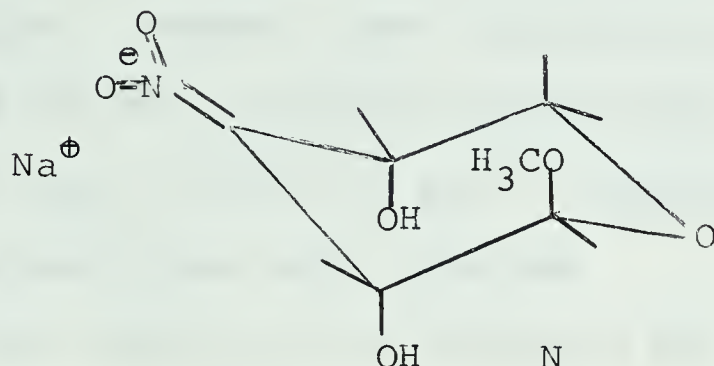
Nitroolefinic sugars have been prepared by the Schmidt-Rutz (74) reaction of the corresponding β -acetoxy-nitrosugars. In this manner, 1-nitro-1,2-unsaturated sugars were prepared by Sowden and Fischer (75) and 3-nitro-2,3-unsaturated sugars by Baer et al. (76,77). These nitroolefins, as may be expected from the behaviour of nitroolefins in general (78), added nucleophilic reagents (70,77).

The aci-nitrosugars formed after condensation of the "sugar dialdehydes" with nitromethane are of some interest since, in each case, only a few of the eight possible diastereoisomeric nitro products were observed. This field has been reviewed by Lichtenthaler (79). Before discussing the product-determining influences experienced in the aci-nitro salts, it is as well to examine the transformation of these salts to the free nitro compounds.

P.M.R. studies (80,81) upon nitrocyclohexane have shown that the conformational free-energy difference for the nitro group is 0.8 to 1.0 kcal/mole. 1-Aci-nitro-2-phenylcyclohexane has been shown (60,82) to give the much less stable cis isomer of 1-phenyl-2-nitrocyclohexane indicating that epimerisation of the nitro function occurs at a negligible rate in acid. Since the products of nitromethane condensation almost invariably have the nitro function equatorially disposed, then the protonation of the aci-nitro form must experience strong steric control. Therefore these products are formed by kinetic control and not thermodynamic control. The acidifications were conducted in mild conditions where the Nef reaction would not be encountered.

The dialdehyde formed on periodate oxidation of methyl β -D-xylopyranoside gave, after equilibration, methyl 3-aci-nitro-3-deoxy- β -D-erythro-pentopyranoside sodium (N) as the main product of condensation (71,83). None of the corresponding α -L-erythro-product was observed, although

smaller amounts of the other two possible isomers were present. For reasons of the exocyclic A^(1,3) effect (60), it can be anticipated that the conformation of the main product will be as shown. Presumably, this conformation



will also be favored for reasons of the anomeric effect (84). The actual conformation has not been determined. The results of the equilibration indicated that N does not correspond to the major product of the ring-closure reaction. Protonation of N gave approximately equal proportions of the β -ribo and β -xylo configurations.

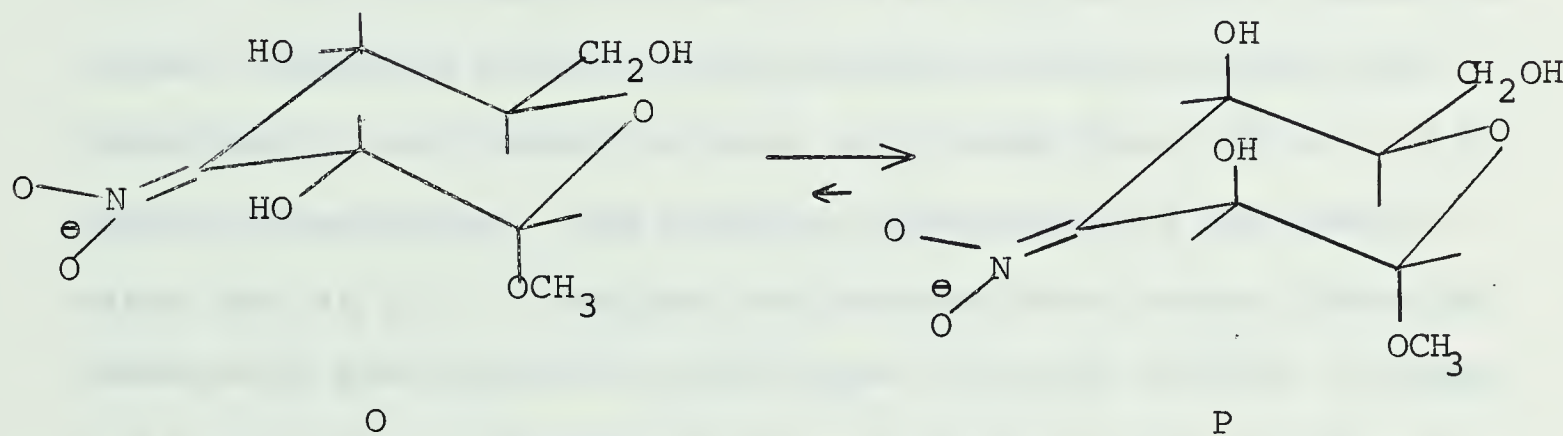
The dialdehyde formed on periodate oxidation of methyl α -D-glucopyranoside gave, after condensation with nitromethane and acidification, approximately 60% gluco and 30% manno (85). This condensation was performed with methanolic sodium methoxide or aqueous potassium hydrogen carbonate. On keeping the aci-nitro salts in water, the product isolated after acidification was 40% talo, 30% galacto, 10-12% manno and traces of gluco.

Similarly, the initial product (86) was 32-40% gluco from the dialdehyde derived from methyl β -D-glucopyranoside. However, on storage of the intermediate aci-nitro salts in aqueous sodium hydroxide before acidifica-

tion, the major product was galacto (34%) together with gluco (25%) and manno (13%). The yield of talo was not stated. In both these 3-deoxy-3-nitrohexopyranoside examples, no compounds were observed with the 3-position in the L-configuration. However, when the same procedure was performed with the dialdehyde derived from levoglucosan (87), which has the ring in the ¹C₄ conformation, the reverse set of configurations were obtained.

This thesis is not concerned with the stereochemistry of the ring-closure reactions involved in the eventual formation of the aci-salts of the 3-nitroglycosides. However, the stereochemistry of the protonation of these aci-salts is pertinent. As was pointed out, in all cases so far reported, the protonation has given the compound which, in the expected chair form, has the nitro group in equatorial orientation. In this regard, Johnson and Malhotra (60) have commented on the protonation of compounds bearing an sp² hybridized system on a cyclohexane ring. The influence of the so-called A^(1,3) effect, according to these authors, forces the group neighbouring the sp² hybridized carbon into an axial disposition, and then the species is protonated in this conformation. Since the approach trans to the neighbouring function is least hindered, the product is a cis-disubstituted cyclohexane. They pointed out that the stereospecific protonation may also arise from steric interactions of the type experienced in the final product being felt in the transition state. The present evidence

does not allow a choice to be made between these two possibilities. That thermodynamic control is rate controlling in these protonation reactions seems to be inferred by the results obtained in the protonation of the aci-salts of 3-nitroglycosides. For example, it can be anticipated that the aci-salt (O) obtained from the condensation with the dialdehyde obtained from methyl α -D-glucopyranoside has the conformation shown, or even perhaps a twist-boat.



The greater stability of the diastereoisomer P, which most likely has the conformation shown, can be attributed to the $A^{(1,3)}$ effect. However, in both cases, axial protonation is the preferred route of reaction. It therefore appears that these reactions avoid the route which would place the nitro group in axial orientation opposing the axial methoxy group. Certainly the factors which govern the stereoselectivity of these protonation reactions require further study.

EXPERIMENTAL

Proton magnetic resonance (P.M.R.) spectra at 60 Mc.p.s. were determined with a Varian A60 spectrometer on CDCl_3 solutions with tetramethylsilane (TMS) as internal reference, or as stated in the text. The P.M.R. spectra at 100 Mc.p.s. were determined with a Varian HR100 (later HD100) spectrometer. Chemical shifts are reported in tau (τ) values with respect to the tetramethylsilane standard.

For the determination of 100 Mc.p.s. P.M.R. spectra, unless otherwise stated, approximately 50 mg of sample was dissolved in sufficient solvent to provide the 0.25 to 0.3 ml solution necessary. The ambient temperature of the spectrometer was $35 \pm 2^\circ$. Cooling and heating were accomplished by passage of pre-cooled or pre-heated nitrogen through a jacket in a special probe containing the spinning tube. Double- and triple-resonance experiments were performed to positively identify signals and splittings of doubtful origin. Often the width of certain signals could be reduced by double resonance, and, in these cases, an upper limit is stated for the long-range coupling constants. The decoupling experiments were originally performed by a field sweep method, but later the spectrometer was modified to allow a frequency sweep technique to be used. The relative signs of the coupling constants were not determined, except in one case, which is described in detail in the text.

Infra-red (I.R.) spectra were obtained with a Perkin-Elmer (Model 421) Grating Spectrophotometer. Unless otherwise stated in the text, I.R. spectra were performed on 10% chloroform solutions in 0.1 mm NaCl cells. The I.R. spectra of some fractions eluted from a gas-liquid chromatograph were recorded with a Wilks Scientific (Model 12) Multiple Internal Reflectance Cell.

Gas-liquid chromatography (g.l.c.) was performed with an F and M (Model 500) Gas Chromatograph, fitted with a thermal conductivity detector. Helium was the carrier gas.

Rotations were measured by a Perkin-Elmer (Model 141) Polarimeter, or followed during reactions by a Rudolph Instruments Engineering Co. Automatic Recording Spectropolarimeter (Model 260/655/850/810-614). The latter apparatus has a water-jacketed tube-container which maintained the tube at a constant temperature.

The refractive indices were measured with a Bausch and Lomb Optical Co. Constant Temperature Refractometer (Model 33-45-58).

Melting points were determined on a Leitz Microscope Heating Stage (Model 350) and, like boiling points, are uncorrected. All temperatures are in degrees Centigrade.

Solvents were evaporated on a rotary evaporator with a maximum bath temperature of 50°, unless otherwise stated.

1. Preparation and P.M.R. Spectra of Glycals.

(a) Preparation of 4,6-O-Benzylidene Glycals

i) 3-O-acetyl-4,6-O-benzylidene-D-glucal (I). - This compound, m.p. 136-7°, $[\alpha]_D^{27} -85^\circ$ (c, 1 in chloroform) was kindly provided by Dr. R. K. Brown and Dr. M. S. Sharma of this Department. The preparation is as yet unpublished and involved a reaction between D-glucal and benzaldehyde in the presence of zinc chloride under rigorously dry conditions, followed by acetylation of the C-3 hydroxyl function with acetic anhydride and pyridine. The P.M.R. parameters are reported later in Table X.

ii) 3-O-Acetyl-4,6-O-benzylidene-D-allal (II) and 4,6-O-benzylidene-D-allal (III) (88). - These compounds were prepared according to the published procedure (88), except in that a Soxhlet system was found unnecessary in the preparation of III. Compound II had m.p. 119.5 - 120.5° and $[\alpha]_D^{25} + 256^\circ$ (c, 0.2 in ethanol), and compound III had m.p. 83.5° and $[\alpha]_D^{25} + 210^\circ$ (c, 2 in ethanol). These physical constants were in excellent agreement with those previously reported (88) which were for II, m.p. 121.0 - 121.5° and $[\alpha]_D^{24} + 253^\circ$ (c, 0.166 in ethanol), and for III, m.p. 84.0 - 84.5° and $[\alpha]_D^{25} + 210^\circ$ (c, 0.44 in ethanol). The P.M.R. parameters are reported later in Table X.

(b) Preparation of Other Glycals Unsubstituted
at the 2-Position

The compounds IV through VIII have all been previously reported. The preparations were changed from the procedure of Helferich et al. (89). In each case, the intermediate acetobromo sugar was isolated before reaction with the zinc-copper dust. All glycals were fractionally distilled at reduced pressure into a receiver cooled in a carbon dioxide-acetone bath and center fractions checked by 60 Mc.p.s. P.M.R. spectroscopy before further use. Distillation invariably gave products of greater purity than those obtained by crystallisation.

i) 3,4-Di-O-acetyl-L-rhamnal (IV) (90). This compound, a syrup, $[\alpha]_D^{25} + 12^\circ$ (c, 1.6 in chloroform), was prepared as above. Although the rotation was appreciably different from that previously reported (90), $[\alpha]_D^{20} + 63^\circ$ (tetrachloroethane), the product obtained after distillation at 110-115° at 0.3 mm was found to be contaminated with approximately only 10% of an impurity, possibly 1,2,3,4-tetra-O-acetyl-L-rhamnal. The identity of the main product was shown by its P.M.R. spectrum (Fig. 2), by the I.R. spectrum (C=C stretch at 1646 cm^{-1}), and by immediate decolorization of a solution of bromine in carbon tetrachloride. The P.M.R. parameters are reported later in Table X.

ii) 3,4,6-Tri-O-acetyl-D-galactal (V) (91). - This compound, m.p. $29 - 30^{\circ}$, $[\alpha]_D^{24} -16.7^{\circ}$ (c, 3 in chloroform), was obtained by distillation at $130 - 135^{\circ}$ at 0.3 mm of the crude product from the preparation as described above. The physical constants were in excellent agreement with the literature values, m.p. 30° , $[\alpha]_D^{20} -16.5^{\circ}$ (c, 3 in chloroform). The P.M.R. parameters are reported later in Table X.

iii) 3,4,6-Tri-O-acetyl-D-glucal (VI) (92). - This compound, m.p. $53 - 54^{\circ}$, $[\alpha]_D^{24} -18.0^{\circ}$ (c, 3 in chloroform), was obtained by distillation at $140 - 145^{\circ}$ at 0.3 mm of the crude product from the preparation as described above. The physical constants were in good agreement with the literature values, m.p. 55° , $[\alpha]_D^{22} -15.7^{\circ}$ (c, 10 in ethanol). The P.M.R. parameters are reported later in Table X.

iv) 4,6-Di-O-acetyl-3-O-methyl-D-glucal (VII) (93). - This compound was prepared from 3-O-methyl-D-glucose by the procedure mentioned above. Glucose gave 1,2:5,6-di-O-isopropylidene- α -D-glucofuranoside by reaction with acetone, phosphoric acid and anhydrous zinc chloride (94). This was then methylated by dimethylsulfate and sodium hydroxide in acetone, and then the isopropylidene functions removed by refluxing with an aqueous suspension of IR-120 resin. This 3-O-methyl-D-glucose had physical constants (m.p. $166-8^{\circ}$, $[\alpha]_D^{26} + 99^{\circ} \rightarrow +56^{\circ}$ eq'l. at 18 hr (c. 3 in water)) in good agreement with those previously reported (94).

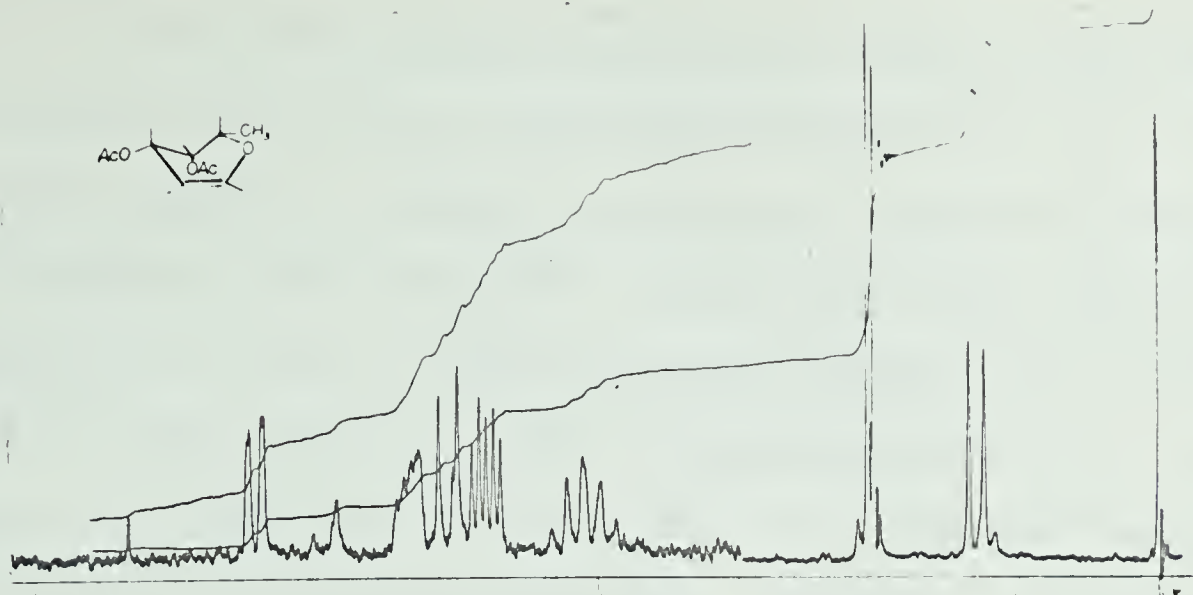


FIG. 2. P.M.R. spectrum (60 Mc.p.s.) of 3,4-di-O-acetyl-L-rhamnal (IV). (Acetoxy and methyl signals at reduced amplitude). EXPERIMENTAL, Section 1.(b)i).

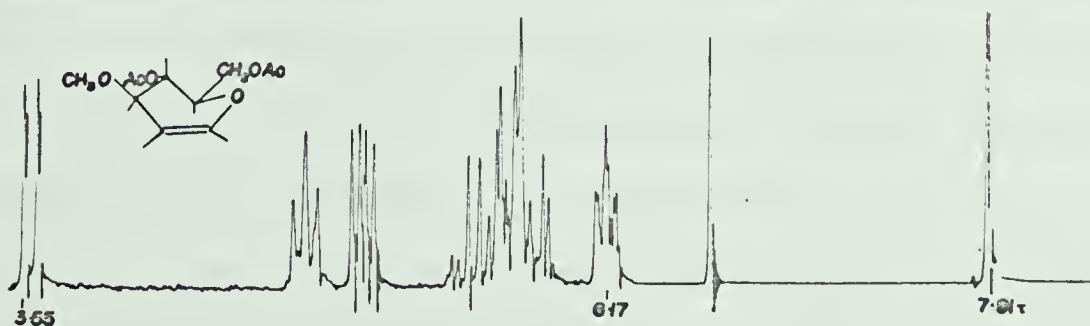


FIG. 3. P.M.R. spectrum (100 Mc.p.s.) of 4,6-di-O-acetyl-3-O-methyl-D-glucal (VII). EXPERIMENTAL, Section 1.(b)iv).

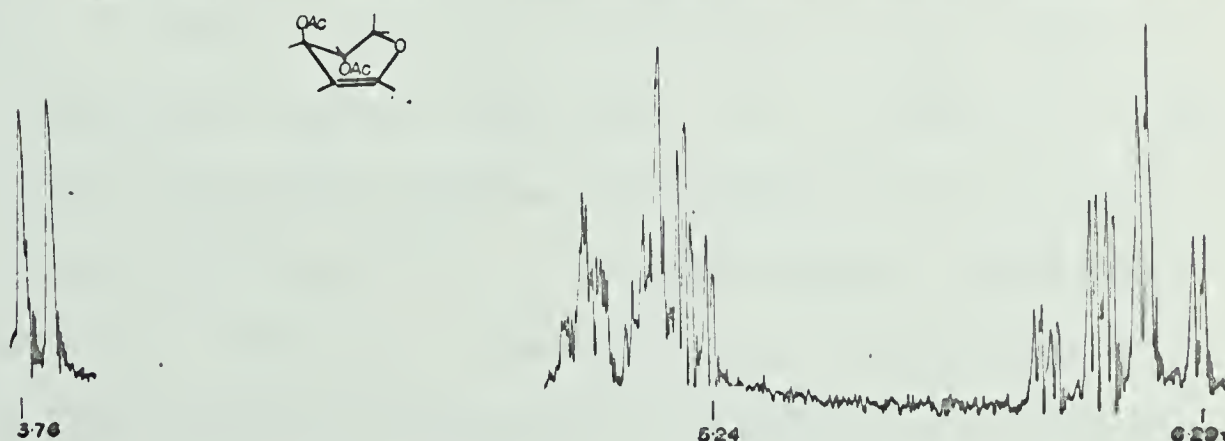


FIG. 4. P.M.R. spectrum (100 Mc.p.s.) of 3,4-di-O-acetyl-D-xylal (VIII). (Acetoxy signals not shown). EXPERIMENTAL, Section 1.(b)v).

The usual procedure gave poor yields of VII from the intermediate 2,4,6-tri-O-acetyl-3-O-methyl- α -D-glucopyranosyl bromide. However, when twice the usual concentration of zinc-copper dust was used, and when the usual ratio of chloroform to water in the isolation procedure was doubled, crude VII was given in a yield of approximately 80%. This product was distilled at 120 - 125° at 0.3 mm and started to crystallise in the cooled receiver. However, on warming to room temperature, the distillate became a mobile, colorless syrup, n_D^{27} 1.4617 and $[\alpha]_D^{24}$ +10° (\underline{c} , 1 in chloroform). The rotation was previously reported (93) as $[\alpha]_D^{20}$ -33.0° (in chloroform). Because of the anomalous rotation, the product was further checked by I.R. spectroscopy, carbon and hydrogen analysis and molecular weight determination, and found to be satisfactory. Also the P.M.R. spectrum, Fig 3 and Table X, clearly indicated that the substance was virtually pure.

v) 3,4-Di-O-acetyl-D-xylal (VIII) (95). - This compound, m.p. 37°, $[\alpha]_D^{23}$ -314° (\underline{c} , 3 in chloroform), was prepared according to the modifications described for VII, and the crude product was rapidly distilled at 95 - 105° at 0.3 mm. The physical constants were in good agreement with those, m.p. 40° and $[\alpha]_D^{25}$ -315° (\underline{c} , 3 in chloroform), previously reported (95). The P.M.R. spectrum, Fig. 4 and Table X, confirms the structure previously assigned to this compound.

(c) Preparation of Glycols with Chloro or Acetoxy
Substituents at the 2-Position

i) 3,4,6-Tri-O-acetyl-2-chloro-D-glucal (IX). - This compound, n_D^{27} 1.4727, $[\alpha]_D^{25}$ +13.4° (c, 2 in chloroform) was prepared by a modification of the published procedure (96).

3,4,6-Tri-O-acetyl-2-chloro-2-deoxy- α -D-glucopyranosyl bromide (97) (560 mg, 1.47 mmole) and tetra-n-butylammonium bromide, (591 mg, 1.83 mmole) were dissolved in pyridine (2 ml). Then triethylamine (0.50 ml, 3.5 mmole) was added and the solution immediately became warm. The solution darkened and deposited white crystals. After 30 min, the crystals were removed by filtration, washed with pyridine and the pyridine solution concentrated. The black syrup was dissolved in toluene and the solution concentrated. Then the syrup was dissolved in 5 ml chloroform, and this solution washed successively with two 10 ml portions of water, three 5 ml portions of N hydrochloric acid and one 10 ml portion of water, then dried with silicic acid. The yellow solution remaining was almost completely decolorized upon a second treatment with dry silicic acid. The solution was concentrated, the pale yellow syrup then dissolved in carbon tetrachloride and this solution concentrated. After removal of residual solvent in vacuo, 291 mg (67%) of IX remained. The P.M.R. spectrum (Table X) showed the product to be virtually pure (see Fig. 27).

ii) 2-Acetoxy-3,4,6-tri-O-acetyl-D-glucal (X). - This compound, a sample of the preparation reported by Lemieux and Lineback (98), had m.p. 61° , $[\alpha]_D^{25} -20^{\circ}$ (\underline{c} , 2 in ethanol).

iii) 2-Acetoxy-4,6-di-O-acetyl-3-O-mesitoyl-D-glucal (XI), and 2-Acetoxy-4,6-di-O-acetyl-3-O-(2,6-dichlorobenzoyl)-D-glucal (XII). - These compounds were samples of the preparations reported by Lemieux and Bose (99). Compound XI had m.p. $114 - 116^{\circ}$, $[\alpha]_D^{23} -39.6^{\circ}$ (\underline{c} , 1.2 in acetonitrile), and XII, a syrup, had $[\alpha]_D^{23} -11.35^{\circ}$ (\underline{c} , 3.13 in chloroform).

2. The Reaction of Acetylated Glycals with Nitrosyl Chloride.

(a) The Reaction of 3,4,6-Tri-O-acetyl-D-glucal (VI) with Nitrosyl Chloride

A three-necked 250 ml flask was equipped with a gas inlet tube, a gas outlet tube, a dropping funnel and a magnetic stirring bar. The gas inlet tube was connected through an empty gas-washing bottle, as a precaution against back-flow, and a gas washing bottle containing granulated anhydrous calcium chloride to a three-way stopcock. This stopcock was connected to cylinders of nitrosyl chloride, (Matheson and Co.) and purified nitrogen.

Methylene chloride (100 ml, reagent grade, dried by passage through a column of previously dried, non-acid washed alumina) was placed in the flask and then the whole system flushed with nitrogen. The flask was cooled in a carbon dioxide - acetone bath to -20° , and then excess nitrosyl chloride condensed in the methylene chloride. This solution was then thoroughly flushed with nitrogen to remove any chlorine (b.p. -35°) that had condensed, (manufacturer's specification for nitrosyl chloride supplied was 93%).

The solution was cooled to approximately -80° in the carbon dioxide - acetone bath, and a solution of VI (5.0 g) in dry methylene chloride (15 ml) added dropwise with stirring. After addition had been completed, the reaction flask was removed from the cooling bath and allowed to reach room temperature. The reaction mixture was continuously flushed with nitrogen throughout this procedure, and helped remove much of the excess nitrosyl chloride. Then the reaction mixture was concentrated at 30° to yield a blue syrup, which was dissolved in warm methylene chloride (15 ml). n-Hexane was added to opalescence, and when the solution was allowed to cool, white needles were obtained. This product was collected by filtration, washed with ice-cold n-hexane and dried in vacuo over anhydrous calcium sulphate. The mother liquor gave a second crop, the combined yield being 5.6 g (90%) of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl chloride (XVII), with a P.M.R. spectrum identical to that of the analytical sample.

After several recrystallisations from ether, the melting point rose from 115° to a constant $129 - 130^{\circ}$. The substance melted to a bubbling blue-green liquid. Compound XVII had $[\alpha]_D^{23} +149^{\circ}$ (c , 2.2 in chloroform). The P.M.R. spectrum (Fig. 5 and Table XII) was as expected for XVII. The I.R. spectrum lacked any indication of the monomeric form (e.g. $-N=O$ stretching at $\sim 1550\text{ cm}^{-1}$).

Anal. Calcd. for $(C_{12}H_{16}NO_8Cl)_2$: C, 42.67; H, 4.74; N, 4.15; Cl, 10.52%; M.W., 675.5. Found: C, 42.50; H, 4.71; N, 4.10; Cl, 10.49; M.W., 600.

Compound XVII slowly decomposed to an oil with the evolution of brown fumes when stored in a stoppered flask. However, it was found to be stable when stored in a Petrie dish in vacuo over potassium hydroxide and phosphorus pentoxide.

(b) The Reaction of 3,4,6-Tri-O-acetyl-D-galactal
(V) with Nitrosyl Chloride

Compound V (5.00 g) was reacted with nitrosyl chloride by the procedure previously described for VI. The yield of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-galactopyranosyl chloride (XVIII) was 5.46 g (88%). XVIII melted, with decomposition, to a blue-green liquid at $128 - 131^{\circ}$, and had $[\alpha]_D^{23} +128^{\circ}$ (c , 2.2 in chloroform). The P.M.R. spectrum (Fig. 6 and Table XII) was as expected for XVIII.

Anal. Calcd. for $(C_{12}H_{16}NO_8Cl)_2$; C, 42.67; H, 4.74; N, 4.15%, M.W. 675.5: Found: C, 42.44; H, 4.78; N, 4.16%, M.W., 674.

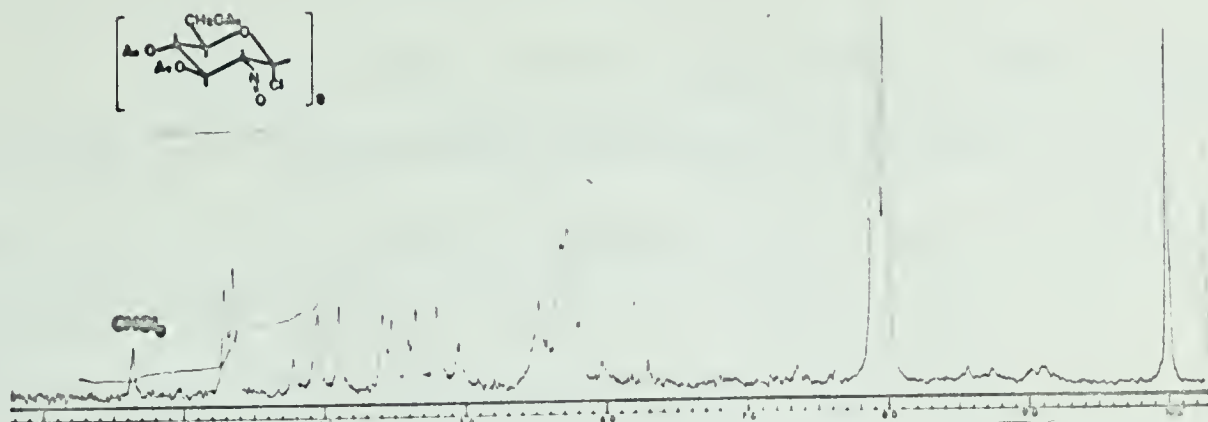


FIG. 5. P.M.R. spectrum (60 Mc.p.s.) of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucosyl chloride (XVII). EXPERIMENTAL, Section 2.(a).

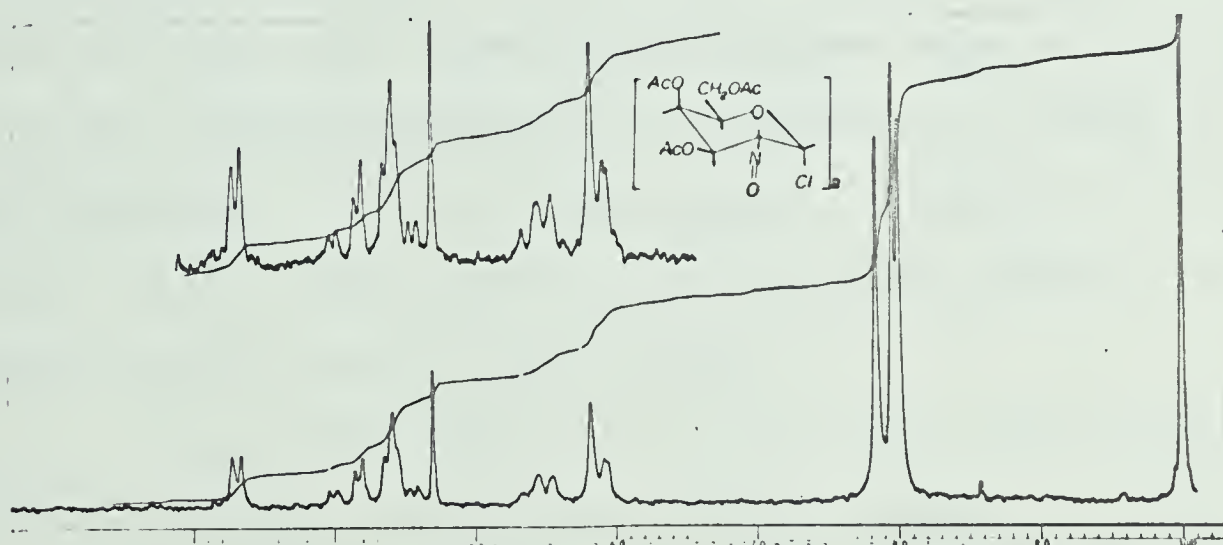


FIG. 6. P.M.R. spectrum (60 Mc.p.s.) of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-galactosyl chloride (XVIII). (Whole spectrum run at same amplitude.) EXPERIMENTAL, Section 2.(b).

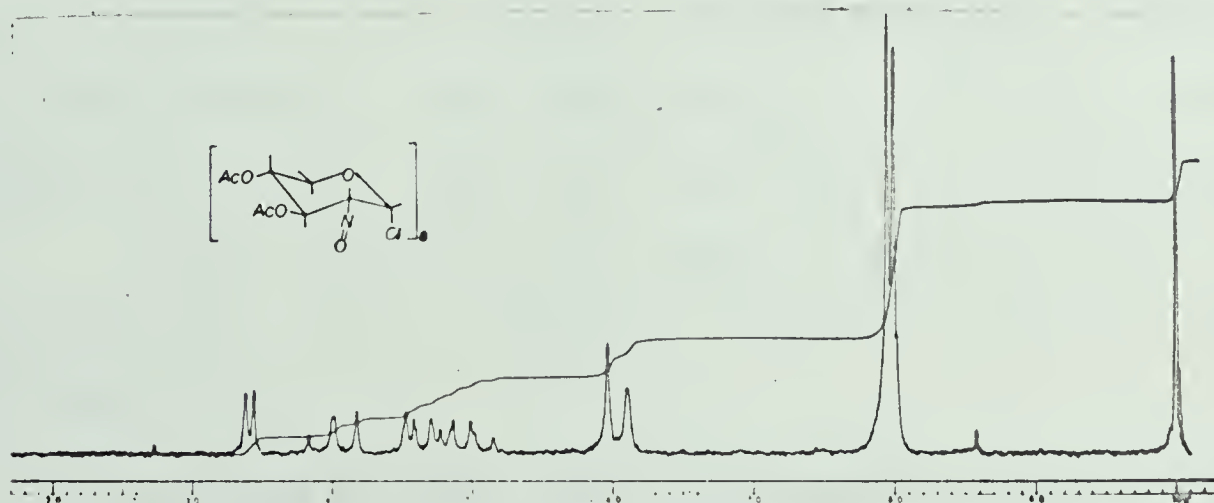


FIG. 7. P.M.R. spectrum (60 Mc.p.s.) of 3,4-di-O-acetyl-2-deoxy-2-nitroso- α -D-xylosyl chloride (XIX). (Whole spectrum run at same amplitude.) EXPERIMENTAL, Section 2.(c).

(c) The Reaction of 3,4-Di-O-acetyl-D-xylal (VIII)
with Nitrosyl Chloride

Compound VIII (4.90 g) was reacted with nitrosyl chloride by the procedure previously described for VI. The yield of 3,4-di-O-acetyl-2-deoxy-2-nitroso- α -D-xylopyranosyl chloride (XIX) was 5.85 g. XIX had m.p. 102 - 106° (blue-green melt, decomposing) and $[\alpha]_D^{23} +164^\circ$ (c , 3.1 in chloroform) after one recrystallisation. The P.M.R. spectrum is reproduced in Fig. 7 and some of the P.M.R. parameters are given in Table XII. Elementary analyses were not obtained since the compound decomposed too readily on attempted purifications. As will be seen below, attempted purification of XIX failed and, instead of the expected product, 3,4-di-O-acetyl-2-nitro-D-xylal was obtained.

In an experiment where 4.00 g VIII was reacted with nitrosyl chloride, wherein an attempt was made to slowly crystallise the reaction product from methylene chloride and n-hexane, a gummy product (4.3 g) was obtained. The syrupy phase was removed on a porous tile and the solid recrystallised from ethyl acetate. The yield was 1.4 g (29%) of a colorless product, m.p. 128-9° and $[\alpha]_D^{23} -319^\circ$ (c , 2.1 in chloroform).

Anal. Calcd. for $C_9H_{11}NO_7$; C, 44.08; H, 4.52; N, 5.71%; M.W., 245.2. Found: C, 44.19; H, 4.54; N, 5.69%; M.W. 237.

As will be seen later, this same material was prepared in high yield from the reaction of VIII with dinitrogen tetroxide.

The oily material defied attempts at crystallisation. The P.M.R. spectrum was indistinct and indicated a mixture.

(d) The Stability of 3,4,6-Tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl Chloride (XVII)

i) In distilling carbon tetrachloride. - Compound XVII

(782 mg) was dissolved in carbon tetrachloride (25 ml) and the solution placed in a distillation apparatus. The carbon tetrachloride was distilled at atmospheric pressure from the solution and collected in a receiver cooled to approximately -80° in a carbon dioxide - acetone bath. Carbon tetrachloride was continually added to keep the solution at a constant level. After approximately 200 ml of distillate had been collected (2 hr), the receiver was removed from the cooling bath. Upon melting of the solid carbon tetrachloride, a brown solution remained which evolved brown fumes at room temperature.

The solution contained in the distillation flask was concentrated to a semi-crystalline material, weight 719 mg. The P.M.R. spectrum of this material showed it to contain 46% 3,4,6-tri-O-acetyl-D-glucal (VI), 46% starting material (XVII) and 8% of a material with a signal at $\tau 1.7$. In the light of the experience with the decomposition of XIX, this latter product was tentatively identified as 3,4,6-tri-O-acetyl-2-nitro-D-glucal (XIII).

ii) In refluxing carbon tetrachloride under a strongly cooled condenser. - Compound XVII (310 mg) was dissolved in carbon tetrachloride (25 ml) and placed in a flask fitted with an

adapted air-cooled condenser. Nitrogen was briefly bubbled through the solution and then the whole system kept under a slight overpressure of dry nitrogen applied at the top of the condenser. The condenser was jacketed with a carbon dioxide - acetone bath, and the carbon tetrachloride solution refluxed for two hr. This solution was then concentrated to a semi-crystalline material, weight 277 mg.

The P.M.R. spectrum of this product showed that it contained 77% starting material (XVII), 15% VI and 8% XIII.

(e) Attempted Diels-Alder Additions to 3,4,6-Tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl Chloride (XVII)

Compound XVII (500 mg, 1.48 mmole and 1,4-diphenyl-1,3-butadiene (340 mg, 1.65 mmole) were dissolved in dry methylene chloride. Nitrogen was briefly bubbled through the solution. A slight overpressure of dry nitrogen was applied at the top of a condenser fitted to the reaction flask, and the solution gently refluxed on a warm water bath for three hr. After standing a further twelve hr at room temperature, the solution was concentrated at 20° to a semi-solid material.

The P.M.R. spectrum of the product showed that neither Diels-Alder addition to XVII, nor decomposition of XVII had occurred.

Similar experiments were performed with slightly more than one equivalent of 2,3-dimethyl-1,3-butadiene and methyl sorbate. A reaction was also attempted with 1,3-butadiene in

a pressure bottle at 20°. The P.M.R. spectra showed the absence of both decomposition and Diels-Alder additions in these cases.

3. The Reaction of Acetylated Glycals with Dinitrogen Tetroxide.

(a) Introduction, Reagents and Techniques

Conditions were found that allowed the production of acetylated 2-nitroglycals and of the corresponding 2-deoxy-2-nitroso- α -nitrates. The nature of both types of compounds required precautions to ensure their stability.

The dinitrogen tetroxide (Matheson and Co.) was allowed to distil out of the lecture bottle in which it was supplied. This cylinder was placed in a bath of water at room temperature to ensure a constant stream of gas; otherwise the initial rapid distillation was followed by a dwindling supply as the remaining liquid cooled. Oxygen was dried by passage through concentrated sulphuric acid in a gas-washing bottle then a trap cooled in a carbon dioxide - acetone bath before admixture with the dinitrogen tetroxide at a Y - connection. These gases then passed through an empty gas-washing bottle (to prevent possible back-flow to the cylinder) before

entering the reaction flask through a wide gas inlet tube dipping beneath the surface of the reaction mixture. A wide gas inlet tube was essential as dinitrogen tetroxide (f.p -11° , b.p. 21° (100)) slowly condensed inside it and restricted the gas flow. All connections were made with Tygon tubing and ground glass joints, and the experiments were conducted in a fume-hood.

Methylene chloride (reagent grade) was dried by passage through a column of previously dried, non-acid-washed alumina. The acetylated glycals were prepared as previously described and dried in vacuo over phosphorus pentoxide before use.

(b) The Preparation of Acetylated 2-Nitroglycals

i) 3,4,6-Tri-O-acetyl-2-nitro-D-glucal (XIII). - Compound VI (3.00 g, 9.5 mmole) was dissolved in dry methylene chloride (50 ml) in the reaction apparatus previously described. This flask was fitted with a -100° to $+50^{\circ}$ thermometer. Then, with the oxygen stream on, the solution was cooled to approximately -80° in the carbon dioxide - acetone bath. Dinitrogen tetroxide was admixed with the oxygen stream for ten min. The initial addition of dinitrogen tetroxide caused a rise in temperature to approximately -70° and this was accompanied by the formation of a very pale blue coloration in the reaction mixture.

The reaction mixture was stirred another ten min with the oxygen stream on and then concentrated in vacuo (bath temperature 25°) to give a green syrup which evolved gases. Dry

carbon tetrachloride was repeatedly evaporated from this product (bath temperature 50°) until the residual syrup, 4.2 g, no longer evolved gases. A yield of 3.46 g was produced when this syrupy material was kept at 50° under 0.3 mm pressure for 24 hr.

The hard glassy material resisted all attempts at crystallisation. Attempted purification by column chromatography failed as the product was strongly absorbed and reacted with traces of water. Attempted distillation at 140° at 10^{-3} mm led to considerable darkening and decomposition. The P.M.R. spectrum (Fig. 8 and Table X) indicated the presence of only one compound and the I.R. spectrum contained strong absorptions for olefinic bond and nitro asymmetric stretching at 1645 cm^{-1} and 1510 cm^{-1} , respectively. Other physical constants were n_D^{27} 1.4884 and $[\alpha]_D^{26}$ -20° (\underline{c} , 3 in chloroform), $[\alpha]_D^{26}$ $+2^{\circ}$ (\underline{c} , 3 in benzene).

Anal. Calcd. for $\text{C}_{12}\text{H}_{15}\text{NO}_9$: C, 45.43; H, 4.77; N, 4.42%; M.W., 317.3. Found: C, 45.37; H, 4.85; N, 4.12%; M.W., 337 (benzene).

The yield was 99%.

ii) 4,6-Di-O-acetyl-3-O-methyl-2-nitro-D-glucal, (XIV). - The reaction of 4,6-di-O-acetyl-3-O-methyl-D-glucal (VII) under the above conditions led to formation of the corresponding dimeric nitrosonitrate XXI, (see following section). Consequently, XIV was produced by the decomposition of XXI in the following manner.

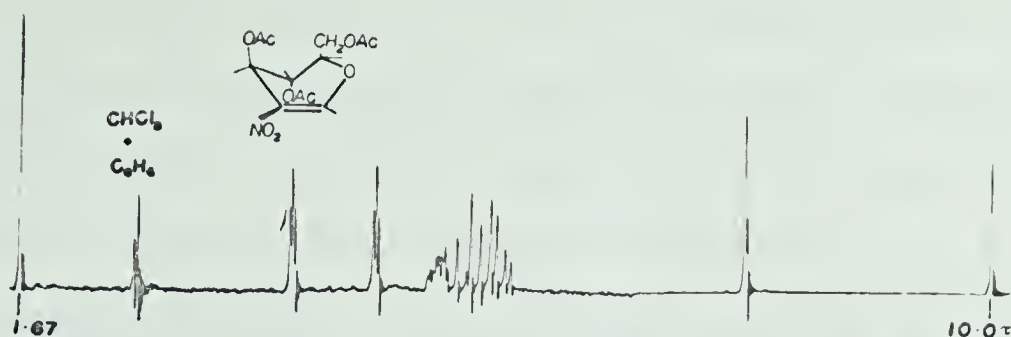


FIG. 8. P.M.R. spectrum (100 Mc.p.s.) of 3,4,6-tri-O-acetyl-2-nitro-D-glucal (XIII).
EXPERIMENTAL, Section 3.(b)i).

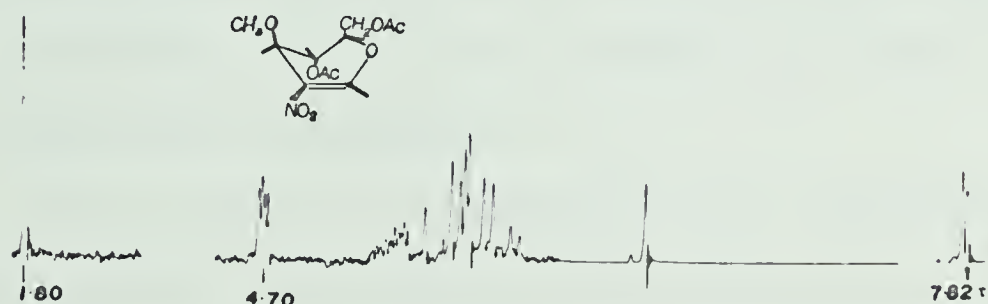


FIG. 9. P.M.R. spectrum (100 Mc.p.s.) of impure 4,6-di-O-acetyl-3-O-methyl-2-nitro-D-glucal (XIV).
(H₁ signal at τ 1.80 is offset).
EXPERIMENTAL, Section 3.(b)ii).

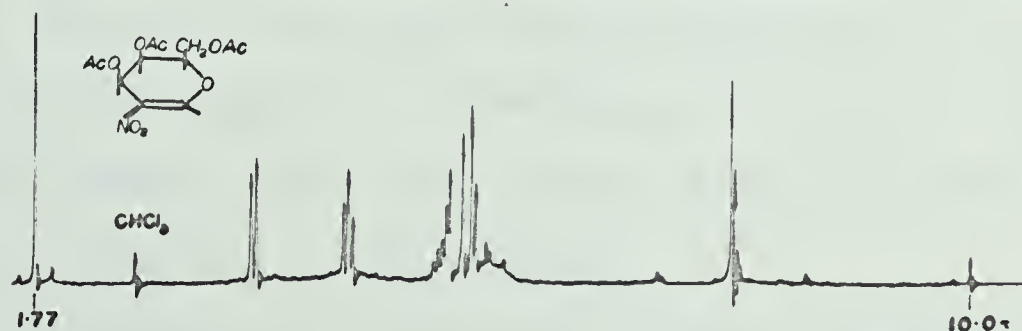


FIG. 10. P.M.R. spectrum (100 Mc.p.s.) of impure 3,4,6-tri-O-acetyl-2-nitro-D-galactal (XV).
EXPERIMENTAL, Section 3.(b)iii).

Compound VII (520 mg, 2.14 mmole) was dissolved in anhydrous diethyl ether (10 ml) and slowly added to a solution of dinitrogen tetroxide and oxygen in ether (30 ml) at approximately 0° (ice-water bath). Stirring and oxygen passage through the mixture was continued throughout the addition and a temperature rise was noted during this process. The cooling bath was removed and the green solution stirred two hr, after which time its temperature had risen to approximately 15°. The solution was concentrated, and dry carbon tetrachloride twice evaporated from the residue to leave a pale blue syrup. The P.M.R. spectrum of this syrup showed that it contained $\sim 2/3$ XXI and $1/3$ XIV, and that the proportion of the latter was increasing.

This syrup was dissolved in dry methylene chloride, the solution kept two days, and then the resulting brown solution concentrated in vacuo at 25°. Dry carbon tetrachloride was twice evaporated from the residue to leave a mobile colorless syrup. When this was kept at 50° and 0.3 mm for 24 hr, 610 mg of a viscous colorless syrup remained. The P.M.R. spectrum (Fig. 9 and Table X) showed traces of an impurity. The I.R. spectrum contained strong absorptions for olefinic bond and nitro asymmetric stretching at 1642 cm^{-1} and 1510 cm^{-1} respectively. The product had n_D^{24} 1.4897 and $[\alpha]_D^{28} +61.2^\circ$ (c , 2.8 in chloroform).

In view of the impurity present, elementary analyses were not made. However, considering the P.M.R. spectrum, a near quantitative yield of the desired compound was undoubtedly obtained.

iii) 3,4,6-Tri-O-acetyl-2-nitro-D-galactal (XV). - 3,4,6-Tri-O-acetyl-D-galactal (V) (6.41 g, 23.6 mmole) was treated with dinitrogen tetroxide and oxygen as previously described in the preparation of XIII. The yield was 7.07 g of a hard glass, n_D^{24} 1.4906 and $[\alpha]_D^{23}$ $+68^\circ$ (c , 3 in chloroform), which failed to crystallise. The P.M.R. spectrum (Fig. 10 and Table X) showed the lack of any impurity, and the I.R. spectrum contained the strong absorptions observed for XIII and XIV. However, satisfactory elementary analyses could not be obtained and the low carbon content was probably due to traces of carbon tetrachloride. The yield was about 94%.

iv) 3,4-Di-O-acetyl-2-nitro-D-xylal (XVI). - 3,4-Di-O-acetyl-D-xylal (VIII) (4.13 g, 20.6 mmole) was treated with dinitrogen tetroxide and oxygen as previously described in the preparation of XIII. The yield was 5.00 g of a slightly oily crystalline material. P.M.R. spectroscopy of this crude product showed ~10% of an impurity with signals at τ 1.9 (a singlet) and τ 4.7 (multiplet). Pure XVI was isolated in the form of long needles by sublimation of the crude product at 110° and 0.3 mm. The yield was 3.91 g of a compound, with $[\alpha]_D^{23}$ -319° (c , 2.1 in chloroform) and a melting point $128-9^\circ$ which was undepressed on admixture with the crystalline product from the decomposition of 3,4-di-O-acetyl-2-deoxy-2-nitroso- α -D-xylopyranosyl chloride (XIX). The P.M.R. spectrum (Fig. 11 and Table X) showed the lack of any impurity.

Anal. Calcd. for $C_9H_{11}NO_7$; C, 44.08; H, 4.52; N, 5.71%; M.W., 245.2. Found: C, 44.19; H, 4.54; N, 5.69%; M.W., 237.

The yield of crystalline product was 77%.

The residue from the sublimation was a hard glass whose molecular weight, 532, viscosity and poor solubility in solvents suggested partial polymerisation.

(c) Preparation of Acetylated 2-Deoxy-2-nitroso- α -hexopyranosyl nitrates

The glycal was dissolved in anhydrous diethyl ether and the solution placed in a three-necked flask equipped with a magnetic stirrer, a gas inlet tube and a gas outlet tube. The flask was cooled in an ice-water bath and the solution briefly oxygenated before the dinitrogen tetroxide - oxygen (approximately equimolar) mixture was passed in. After excess dinitrogen tetroxide (estimated by prior calibration of the valve setting) had been condensed, the brown solution was allowed to stir with continued passage of oxygen for the time indicated.

After removing the cooling bath, most of the ether was evaporated using a rapid stream of oxygen. Enough methylene chloride was then added to dissolve any precipitated material, and the solution was added to a large excess of n-hexane cooled in an ice-water bath. The crystalline precipitate was collected by filtration. Occasionally, seeding or scratching was required to effect crystallisation.

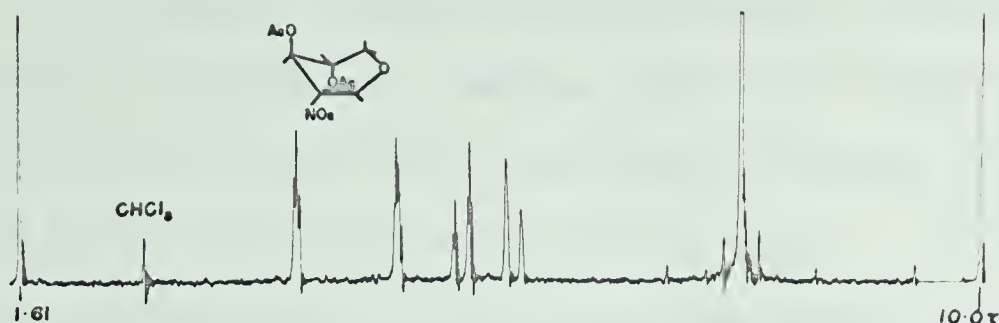


FIG. 11. P.M.R. spectrum (100 Mc.p.s.) of 3,4-di-O-acetyl-2-nitro-D-xylal (XVI). (Acetoxy signals at same amplitude as those of the ring-protons). EXPERIMENTAL, Section 3.(b)iy).

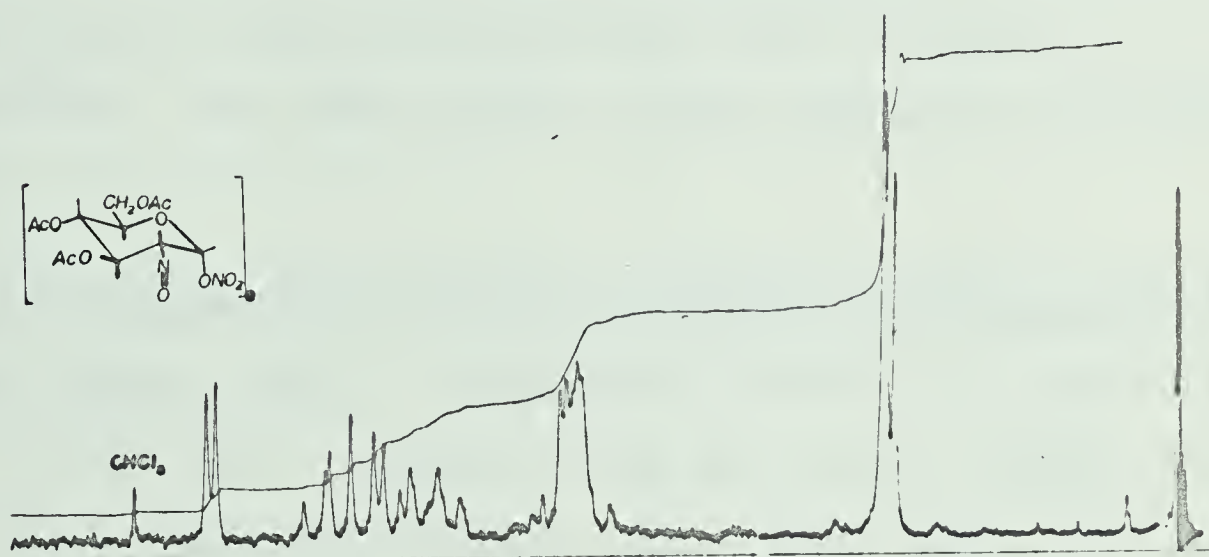


FIG. 12. P.M.R. spectrum (60 Mc.p.s.) of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucosyl nitrate (XX). EXPERIMENTAL, section 3.(c)i).

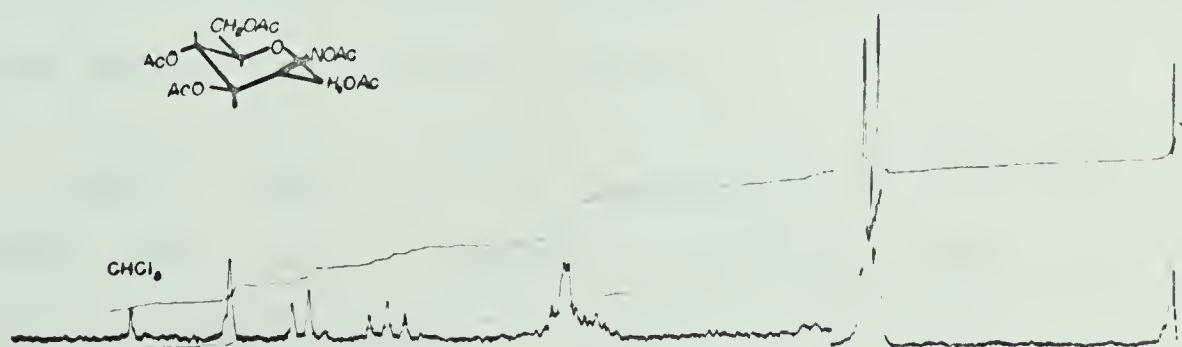


FIG. 13. P.M.R. spectrum (60 Mc.p.s.) of penta-O-acetyl-2-oximino-D-glucopyranose (XXIII). EXPERIMENTAL, Section 3.(d).

The product was recrystallised from methylene chloride and n-hexane. Analytical samples had to be freshly prepared and protected from heat until the actual moment of combustion. These compounds could be stored in the dark at -20° indefinitely, or at room temperature in vacuo over phosphorus pentoxide and potassium hydroxide. When stored in a stoppered flask at room temperature, these compounds rapidly decomposed to syrups, whereas no visible changes occurred in vacuo. Melting points are recorded for determinations with slow increases in temperature. All three melted to give bubbling blue-green liquids.

i) 3,4,6-Tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl nitrate (dimer) (XX). - Compound VI (4.00 g) in anhydrous ether (50 ml) with a reaction time of four hr, yielded 4.91 g (91%) of a crystalline product, m.p. $120-1^{\circ}$ and $[\alpha]_D^{27} +165^{\circ}$ (c, 1.7 in chloroform). The I.R. spectrum contained a broad nitrate absorption band centered at 1680 cm^{-1} and the P.M.R. spectrum is reproduced in Fig. 12. It may be compared with that of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl chloride (dimer) presented in Fig. 5.

Anal. Calcd. for $(C_{12}H_{16}N_2O_{11})_2$: C, 39.56; H, 4.43; N, 7.69%; M.W., 728.6. Found: C, 39.63; H, 4.53; N, 7.33%; M.W. 701 (in chloroform).

Attempts to short cut the above isolation procedure by concentrating the reaction mixture to syrup caused extensive decomposition to the 2-nitroglucal XIII .

ii) 4,6-Di-O-acetyl-2-deoxy-3-O-methyl-2-nitroso- α -D-glucopyranosyl nitrate (dimer) (XXI). - Compound VII (403 mg) in anhydrous ether (20 ml) with a reaction time of one hr gave 330 mg of a compound, m.p. 114 - 115° (dec.), $[\alpha]_D^{27} +222^\circ$ (c , 3.2 in chloroform). The I.R. spectrum contained a broad band for absorption by nitrate centered at 1680 cm^{-1} . The P.M.R. parameters are given in Table XIII.

Anal. Calcd. for $(\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_{10})_2$: C, 39.29; H, 4.80; N, 8.33%; M.W., 672.6. Found: C, 39.50; H, 4.77; N, 8.02%; M.W., 665.

The yield was 58%.

iii) 3,4,6-Tri-O-acetyl-2-deoxy-2-nitroso- α -D-galactopyranosyl nitrate (dimer) (XXII). - Compound V (1.72 g) in anhydrous ether (30 ml) with a reaction time of 1.5 hr yielded 1.18 g of a crystalline product, XXII, m.p. 123-4° (dec.) and $[\alpha]_D^{27} +187^\circ$ (c , 2.6 in chloroform). The I.R. spectrum contained a broad nitrate absorption band centered at 1680 cm^{-1} . The P.M.R. spectrum was similar to that of the nitrosochloride analogue, XVIII, and the parameters are given in Table XIII.

Anal. Calcd. for $(\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_{11})_2$: C, 39.56; H, 4.43; N, 7.69%; M.W., 728.6. Found: C, 39.55; H, 4.56; N, 7.83%; M.W., 725.

iv) 3,4-di-O-acetyl-2-deoxy-2-nitroso- α -D-xylopyranosyl nitrate. - Several attempts to prepare this compound were unsuccessful. In one experiment, a few white crystals were deposited on the walls of the reaction flask from a blue-green solution, and these decomposed into a bubbling syrup

upon achieving room temperature. The marked instability parallels that of the analogous nitrosyl chloride addition compound (see EXPERIMENTAL section 2).

(d) Penta-O-acetyl-2-oximino-D-glucopyranoside
(XXIII) (10)

3,4,6-Tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl nitrate (XX) (364 mg, 1.00 mmole) was placed in a flask with freshly distilled acetic anhydride (8 ml). The flask was equipped with a magnetic stirring bar, serum cap and protective drying tube. Stirring at room temperature caused compound XX to dissolve, providing a pale green solution. The flask was then cooled to -5° , and dry triethylamine (140 μ l, 1 mmole) was injected slowly. During the reaction, (2 hr) an initial dark blue-green color was replaced by a pale yellow coloration. Diethyl ether (20 ml) was added and the solution washed twice with 4 ml portions of water. The ether layer was then dried over anhydrous sodium sulfate, the ether solution decanted and the dessicant washed with more ether. The combined ether portions were concentrated and the remaining acetic anhydride was removed by repeatedly dissolving the residue in m-xylene and reconcentrating until there was no odour of acetic anhydride. The m-xylene was removed by repeating this process with carbon tetrachloride, and the residual solvent removed by placing the syrup in vacuo. The yield was 374 mg of a viscous syrup, $[\alpha]_D^{25} +31.7^{\circ}$ (c, 3.5 in chloroform).

The P.M.R. spectrum (Fig. 13) showed the following chemical shifts (τ value): H_1 , 3.35; H_3 , 3.84; H_4 , 4.46; H_5 and two H_6 , 5.5 - 6.1; two acetyls at 7.84, one at 7.87, two at 7.93. Coupling constants (c.p.s.) were: $J_{3,4}$ 7.5, $J_{4,5}$ approx. 8.0. The I.R. spectrum contained a broad, weak C=N stretching at 1645 cm^{-1} , C-OAc at $1740\text{--}1765\text{ cm}^{-1}$ and C=N-OAc at 1780 cm^{-1} (101), and no absorptions for the nitro group. These properties were identical with those reported (10, 13) for XXIII produced from a similar reaction with 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucopyranosyl chloride (XVII).

Anal. Calcd. for $C_{16}H_{21}NO_{11}$: C, 47.64; H, 5.25; N, 3.47%; M.W., 403.3. Found: C, 47.94; H, 5.29; N, 3.55%; M.W., 385.

The nitroso-nitrate (XX) was also converted to XXIII using sodium acetate-acetic anhydride (10). After dilution of the reaction mixture with ether, the sodium acetate and sodium nitrate were removed by filtration. This inorganic mixture, as an aqueous solution, gave a negative test for nitrite with acidified aqueous NaI solution. The presence of nitrate ion was indicated by adding the material to diphenylamine in 98% H_2SO_4 to produce a dark blue coloration (102).

(e) The Stability of Nitrosonitrate XX under the Conditions Used for the Preparation of 3,4,6-Tri-O-acetyl-2-nitro-D-glucal (XIII)

The flow of dinitrogen tetroxide was calibrated by opening the valve to a selected setting and condensing the dinitrogen tetroxide in a flask containing 1,4-dioxan.

During this time, the cylinder was placed in a water bath, and oxygen was admixed with the dinitrogen tetroxide (both as previously described) to reproduce reaction conditions. 1,4-Dioxan formed a complex with dinitrogen tetroxide that was stable enough (103) to permit weighing of the solution. Average flow of dinitrogen tetroxide was 85 mg per minute.

During the following experiments, the reaction mixtures were exposed to ordinary laboratory and fume-hood illumination from fluorescent lighting. All precautions were taken to keep the conditions anhydrous.

3,4,6-Tri-O-acetyl-D-glucal (VI) (399 mg, 1.47 mmole) was dissolved in dry methylene chloride (30 ml) and the reaction flask cooled to approximately -80° . While the solution was stirred magnetically, dinitrogen tetroxide was passed in at the calibrated rate for five minutes to provide about 400 mg (approximately four mmole). After stirring for five minutes, the solution was concentrated (bath temperature 25°) to give a pale blue oil. Dry carbon tetrachloride (25 ml) was evaporated from the product, and the remaining syrup (weight 891 mg) was examined by P.M.R. spectroscopy. The spectrum revealed that only XIII was present.

When XX (397 mg, 1.09 mmole of monomer) was dissolved and treated as above, the product was 406 mg of crystalline material. P.M.R. spectroscopy showed it to be essentially XX with a small trace of XIII (<10%). After standing five minutes in the P.M.R. tube, the proportion of XIII had increased to ~30%.

(f) Reaction of 3,4,6-Tri-O-acetyl-2-deoxy-2-nitroso-
 α -D-glucopyranosyl Chloride (XVII) with AgNO_3

Compound XVII (337 mg, 1.00 mmole) was dissolved in acetonitrile (10 ml, dried by two distillations from anhydrous K_2CO_3) and treated with a solution of silver nitrate (179 mg, 1.05 mmole) in dry acetonitrile (5 ml). Precipitation commenced immediately, and after 30 minutes shaking, the reaction mixture was centrifuged. However, precipitation was still occurring, so the solution was kept at 50° for a few minutes. After this treatment, no further precipitation occurred and the precipitate was removed by filtration. The filtrate was concentrated to a syrup, weight 351 mg, which appeared to be decomposing (evolution of nitrogen oxides). The I.R. spectrum indicated that little, if any, XX was present (weak nitrate absorption at 1680 cm^{-1}) and that this product contained much 2-nitroglucal XIII (strong $\text{C}=\text{C}$ and NO_2 asymmetric stretching bands.) The rotation of the product - $[\alpha]_{\text{D}}^{26} +10^\circ$ (c , 5 in chloroform) - indicated that little α -glucosyl halide or nitrate was present.

In a second experiment, a five minute reaction gave a syrupy product, the P.M.R. spectrum of which showed it to be an about equimolar mixture of the tri-O-acetyl-2-nitro-D-glucal (XIII) and the starting material (XVII).

(g) The Reaction of 3,4,6-Tri-O-acetyl-D-glucal (VI)
 with Dinitrogen Trioxide and Dinitrogen Pentoxide

Dinitrogen trioxide (Matheson & Co.) was allowed to

distil from a lecture bottle and admixed with nitric oxide (Matheson & Co.) before condensation in dry methylene chloride (40 ml) cooled to approximately -80° in the previously described apparatus. Compound VI (2.00 g) was added slowly from a dropping funnel as a 10% w/v methylene chloride solution. After concentration, 2.30 g of an oil remained which continuously evolved oxides of nitrogen. The P.M.R. spectrum of this material had very poor resolution and no distinct ring-proton signals could be identified. A repeat of this experiment again gave a product with a poorly-defined spectrum.

Dinitrogen pentoxide was prepared from fuming nitric acid and phosphorus pentoxide (104) and sublimed at room temperature in a stream of oxygen into methylene chloride (50 ml) cooled to 0° in an ice-water bath. Compound VI (5.0 g) was slowly added as a 10% w/v methylene chloride solution from a dropping funnel. The reaction mixture was concentrated in vacuo at 50° , and carbon tetrachloride evaporated from the residue to leave 7.3 g of semi-crystalline material. P.M.R. spectroscopy of the product revealed ~30% of 3,4,6-tri-O-acetyl-2-nitro-D-glucal (XIII). This proportion increased with repeated evaporation of carbon tetrachloride from the residue.

When this product was treated with pyridine, XIII was the only carbohydrate material remaining.

(h) An Investigation of the Reaction of VI with
Dinitrogen Tetroxide at -80° in Methylene Chloride

All reagents were carefully dried before use and, unless otherwise stated, all experiments were performed under ordinary laboratory illumination.

i) Control reactions. - Compound VI (342 mg, 1.2 mmole) was dissolved in dry methylene chloride (30 ml). The solution was cooled to approximately -80° and reacted with oxygen and dinitrogen tetroxide (calibrated flow for five minutes) as previously described. After keeping for 20 minutes under these conditions, the reaction mixture was worked up in the usual manner. The product, 611 mg, possessed the P.M.R. spectrum expected for XIII.

In a second experiment, dry VI (1.524 g) was dissolved in dry methylene chloride (30 ml) and the solution treated with dinitrogen tetroxide and oxygen at -80° as previously described. After ten minutes, a sample was withdrawn, placed in a P.M.R. tube and the tube sealed. The tube was kept in a carbon dioxide - ethanol bath throughout, then placed briefly in a cold water bath, dried and placed in the P.M.R. spectrometer.

A spectrum (external TMS standard) was run immediately and then again after twenty minutes. No change was observed between the two, and both distinctly showed XIII to be the only product present.

ii) The effects of changed reaction conditions. - The following experiments were performed with VI (330 ± 10 mg) in dry methylene chloride (30 ml) as described in the former experiment above. Light and oxygen were carefully excluded where indicated in Table I. In the two experiments indicated, tetramethylammonium chloride (413 mg, 3.8 mmole) and tetrachlorohydroquinone (25 mg, 0.1 mmole) were used. In the latter case, most of this inhibitor appeared to precipitate upon lowering the temperature to -80° .

TABLE I

The Products of the Reaction between 0.04M Tri-O-acetyl-D-glucal (VI) and 0.15M Dinitrogen Tetroxide in Methylene Chloride at -80°

<u>Reaction Conditions</u>			<u>Product Composition (mole %) ^a</u>	
<u>Oxygen</u>	<u>Light</u>	<u>Additive</u>	<u>[XIII]</u>	<u>[XX]</u>
+	+	-	100	0
-	+	-	100	0
+	-	-	93	7
-	-	-	70	30
+	-	<u>b</u>	50	50
+	-	<u>c</u>	40	60

a. These values were estimated from integration of 60 Mc.p.s. P.M.R. spectra and are not accurate to within more than a few per cent.

b. 1.2M tetramethylammonium chloride.

c. <0.003 M tetrachlorohydroquinone.

(j) Configurations of Acetylated 2-Nitroglycals

XIII and XV

These compounds were treated as follows. The 2-nitroglycal, (~1 g, ~3 mmole) as a solution in 30 ml of 50% aqueous tetrahydrofuran, was kept at 50° until I.R. spectroscopy showed that only saturated nitro compounds were present (24 hr). The products were hydrogenated at atmospheric pressure over 5% palladium-charcoal in tetrahydrofuran containing

an excess of N hydrochloric acid. The uptake effectively ceased after 30 - 50% of the theoretical volume had been absorbed. The catalyst was then removed by filtration through a bed of Celite supported on a sintered glass funnel and the solution, with washings, was concentrated in vacuo. Little further hydrogenation of this material took place when a fresh portion of catalyst was used.

The remaining brown syrup was kept at 100° in 10 ml of conc. hydrochloric acid for one hour, the solution concentrated in vacuo, and the black syrup taken up in water for decolorization with charcoal. The solution was again concentrated, and the product taken up in 98% ethanol and a small portion degraded with ninhydrin (105) for 18 hr in a sealed tube at 100°.

After removing the black precipitate by filtration, the solution was concentrated in vacuo and applied to Whatman no. 1 paper, together with samples of all four known pentoses. The bottom end of the paper was serrated and then the paper eluted with ethyl acetate - pyridine - water (8:2:1) for 10 hours. The chromatograms were dried and developed with the silver nitrate - sodium hydroxide spray reagent (106).

Compound XIII yielded arabinose and possibly a trace of ribose. Compound XV yielded lyxose and xylose with the former predominating. Thus XIII and XV had the same C-4 and C-5 configurations as parent tri-O-acetylglycals VI and V, respectively. Furthermore, the P.M.R. parameters of XIII and XV support these assignments. The configuration at the 3-position followed from the P.M.R. spectra and conformational properties of the nitroglycals (DISCUSSION, section 1).

4. Reaction of 3,4-Di-O-acetyl-2-nitro-D-xylal (XVI)
with Methanol. Kinetic Investigation of the
Initial Reaction.

(a) Preparation of Reagents

All reagents used in this investigation were dried and then stored under anhydrous conditions. All distillations were performed at atmospheric pressure, unless otherwise stated. All boiling points agreed with those commonly found in the literature.

Methyl and ethyl alcohols were partially reacted with magnesium turnings, and then the excess of alcohol distilled from the slurry of magnesium alkoxide.

Benzyl alcohol was similarly treated with small pieces of sodium metal before distillation.

2-Propanol and 2-chloroethanol were dried with anhydrous sodium carbonate before distillation from a fresh portion of this dessicant.

Dry trichloroacetic acid, 2,2-diphenylethanol (m.p. 67 - 68°), p-methoxybenzyl alcohol (m.p. 23 - 24°) and p-nitrobenzyl alcohol (m.p. 91 - 92°) were obtained by placing the commercial products in vacuo over phosphorus pentoxide at room temperature for one day.

Dimethylsulfoxide, tetrahydrofuran and 1,4-dioxan were allowed to stand three days over calcium hydride before distillation from this dessicant. The fraction of distilled dimethylsulfoxide that was used boiled at 52 - 55° (0.3 mm).

Benzene was dried over sodium wire before distillation.

N,N-dimethylformamide, triethylamine, 2,4,6-collidine, 2,6-lutidine, 2-picoline and pyridine were dried over potassium hydroxide pellets and distilled from a fresh portion of this dessicant. The 2,4,6-collidine had the expected P.M.R. spectrum.

(b) The Polarimetric Technique

The reagents were mixed each time in an order that permitted the maximum accuracy in estimation of their concentrations, but also minimized the time elapsed before the rotation of the reaction mixture could be followed. Factors such as solubility and reaction rapidity often dictated the order of mixing of reagents. Where small volumes of a reagent were needed, a larger volume of a dilute solution of that reagent was used for the purpose of accuracy. In every case, the required amount of sublimed 3,4-di-O-acetyl-2-nitro-D-xylal (XVI) was weighed into the 2.0 ml volumetric flask, and then placed in vacuo over phosphorus pentoxide until it was to be used.

After the reagents were mixed, the drive mechanism of the previously described recording spectropolarimeter was started. After adjusting the volume of the reaction mixture to 2.0 ml, this solution was used to fill a 10 cm polarimeter tube (capacity ~1.4 ml). When the tube was placed in the spectropolarimeter, the recorder was started. Prior to each run, the rotation of the same tube filled with benzene was recorded to provide a zero trace. All rotations were recorded at a wavelength of 589 mμ, with the tube and contents thermostatted at 26°.

The initial polarimetric rate of reaction (P deg/min) was determined by extrapolation of the recorded rotation to zero time. This was done by constructing a tangent to the curve. Since the rotation could be recorded within a few minutes of mixing, and since the curvature of the recorded line was small during the first 20 minutes, this extrapolation was considered to provide a good approximation to the actual initial polarimetric rate. The initial rates of reaction (R) in moles per liter per second were then calculated from the expression,

$$R = \frac{P \ C}{60 \ \Delta} ,$$

where C is the initial concentration of the reactant (XVI) and Δ is the difference between the observed initial rotation and the rotation of the product. In all cases the rotation of the product was assumed to be that of the methyl 4-O-acetyl-2,3-dideoxy-2-nitro- β -D-glycero-pent-2-enopyranoside (XXIV) measured in chloroform.

Definite solvent effects were seen in the observed rotations at zero reaction time. However, these changes were small in relation to the values of the observed rotation and were consistent within a series of conditions where only one reagent concentration was being changed.

(c) The Influences of Co-solvent, Base and Acid

i) Effect of co-solvent. - Compound XVI (40.0 ± 0.1 mg, 0.163 ± 0.0003 mmole) was dissolved in a small volume of the solvent. The methanol (0.40 ml, 9.9 mmole) was then added and the total volume adjusted to 2.0 ml with more of the

TABLE II

The Influence of Co-solvent on the Rate of the Reaction between
Di-O-acetyl-2-nitro-D-xylal (XVI) and Methanol

Co-solvent (v/v) ^a	Initial Polarimetric Rate (deg min ⁻¹) ^b	Initial Rate (mole liter ⁻¹ sec ⁻¹) ^c	Relative Rate
DMSO ^d	+0.0640	1.1×10^{-5}	2.30
Methanol	+0.0364 ^e	6.3×10^{-6}	1.31
50% DMSO ^d , 50% benzene	+0.0352	6.1×10^{-6}	1.27
Benzene	+0.0278	4.9×10^{-6}	1.00
DMF ^f	+0.0166	2.9×10^{-6}	0.60
33% THF ^g , 67% benzene	+0.0040	6.9×10^{-7}	0.14
1,4-dioxan	+0.0024	4.2×10^{-7}	0.09
THF ^g	+0.0015	2.6×10^{-7}	0.05

a. Solvent; 20% methanol plus ~78% of the stated co-solvent.

b. The concentration of XVI was 0.082M. The concentration of methanol was 5.0M except where it was the solvent (27M).

c. Based on the average initial observed rotation -5.9° .

d. Dimethylsulfoxide.

e. One-fifth of initial polarimetric rate.

f. N,N-Dimethylformamide.

g. Tetrahydrofuran.

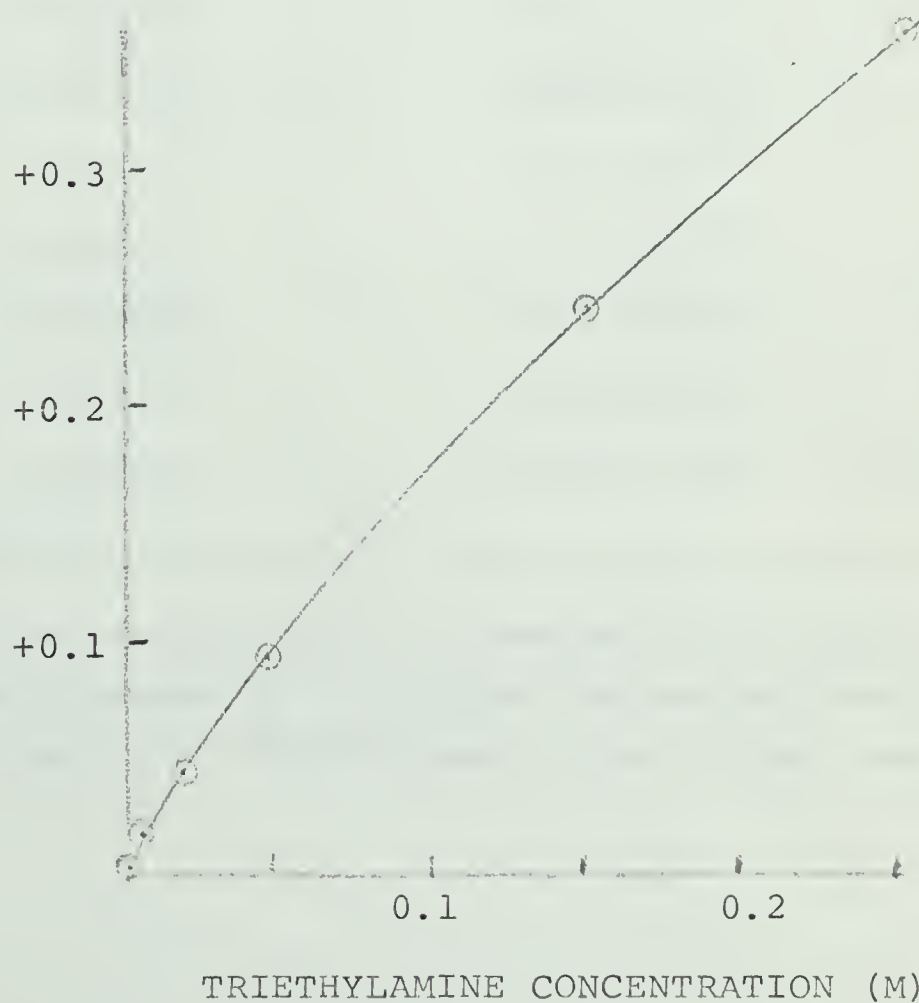
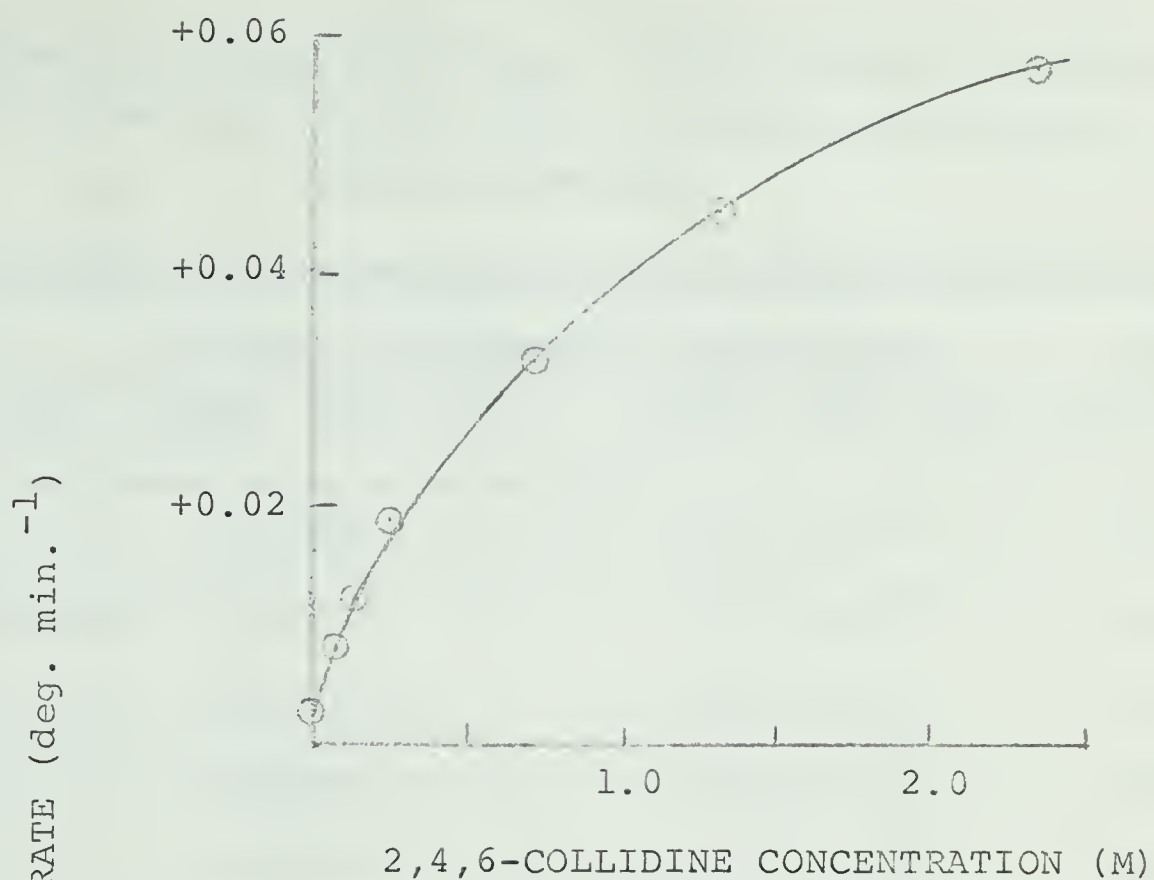


FIG. 14. The effect of 2,4,6-collidine and triethylamine on the initial polarimetric rate of Reaction of 3,4-di-O-acetyl-2-nitro-D-xytal (0.050M) with methanol (1.25M) in benzene at 26°.

TABLE III

The Influence of Base on the Rate of the Reaction between
Di-O-acetyl-2-nitro-D-xylal (XVI) (0.050M) and Methanol
(1.25M) in Benzene

<u>[Base]</u> (mole liter ⁻¹)	<u>Initial Polarimetric</u> <u>Rate</u> (deg min ⁻¹)	<u>Initial Rate</u> (Mole liter ⁻¹ sec ⁻¹) ^a	<u>Relative</u> <u>Rate</u>
0	+0.0030	5.3 x 10 ⁻⁷	1.0
0.063 collidine	+0.0080	1.5 x 10 ⁻⁶	2.8
0.123 "	+0.012	2.2 x 10 ⁻⁶	4.2
0.24 "	+0.019	3.5 x 10 ⁻⁶	6.6
0.69 "	+0.032	5.9 x 10 ⁻⁶	11.1
1.35 "	+0.045	8.3 x 10 ⁻⁶	15.7
2.36 "	+0.057	1.06 x 10 ⁻⁵	20.0
0.0050 Et ₃ N	+0.019	3.0 x 10 ⁻⁶	6.3
0.020 "	+0.044	7.0 x 10 ⁻⁶	13.2
0.050 "	+0.095	1.51 x 10 ⁻⁵	28.5
0.150 "	+0.240	3.81 x 10 ⁻⁵	71.8
0.255 "	+0.357	5.66 x 10 ⁻⁵	106.7

^a. The initial observed rotation in neutral conditions was -3.6°, in the presence of collidine the average was -3.5°, and in the presence of triethylamine the average was -4.1°.

solvent. The results are presented in Table II.

ii) Effect of 2,4,6-collidine. - Compound XVI (24.5 ± 0.1 mg, 0.100 ± 0.0004 mmole) was weighed into the 2.0 ml volumetric flask. A measured volume of 2,4,6-collidine was injected into the flask, the weight of base found by difference, and the mixture then dissolved in approximately 1 ml benzene. A 5.00M solution of methanol in benzene (0.50 ml, 2.5 mmole methanol) was then added and the volume adjusted to 2 ml. The observed polarimetric change with time is reported in Table III.

iii) Effect of triethylamine. - The same procedure was adopted for the study of the influence of added triethylamine. However, as much smaller concentrations were required, the triethylamine was added as a 10% w/v solution in benzene.

The results (Table III) are shown graphically in Fig. 14.

iv) Effect of other bases. - The same procedure was adopted as in ii) with 0.50 mmole of base being added to the previously tared XVI and the weight of base being found by difference. The results are reported in Table IV.

v) Effect of acids. - The acetic acid (0.50 ml, 8.7 mmole) was added neat after dissolution of XVI in benzene. The trichloroacetic acid was added as 1.0 ml of a 1.48M solution in benzene. The kinetic results are reported in Table IV.

The reaction mixture containing trichloroacetic acid was concentrated after a reaction time of 800 min (obs. rotn. -0.35°). The residue was dissolved in carbon tetrachloride, the solvents removed and the residue examined by P.M.R.

spectroscopy in deuteriochloroform. This revealed a mixture of the first-formed product, XXIV (major component), and XVI and XXV (both minor components).

(d) Influences of Alcohol Concentration and Structure

i) Change in methanol concentration. - Compound XVI, (40.0 mg, 0.163 mmole) was weighed into the 2.0 ml volumetric flask, dissolved in benzene, and then aliquots (0, 60 or 150 μ l) of methanol added. The reaction mixture was then adjusted to the standard mark with benzene. The results are presented in Table V.

ii) Change in methanol concentration using 2,4,6-collidine as catalyst. - Compound XVI, (24.5 mg, 0.100 mmole) was weighed into the 2.0 ml volumetric flask, a known volume of 2,4,6-collidine injected into the flask and its weight found by difference. This mixture was then dissolved in approximately 1 ml of benzene, and aliquots (0, 0.10 or 0.25 ml) of the 5M methanol in benzene solution added. The reaction mixture volume was then adjusted to the standard mark with benzene. The results are presented in Table V.

iii) Effect of alcohol structure (neutral conditions). - Compound XVI (40.0 mg, 0.163 mmole) was weighed into the 2.0 ml graduated flask and dissolved in approximately 0.5 ml benzene. Then the alcohol (9.9 mmole) which had been weighed out separately in another flask, was transferred, together with benzene washings, to the graduated flask, and the volume of reaction mixture adjusted to the standard mark with benzene. The results are presented in Table VI.

TABLE IV

The Influence of Acids and Bases upon the Reaction of Di-O-acetyl-2-nitro-D-xylal (XVI) with Methanol.

Acid or Base	Initial Specific Rotation (deg)	Initial Polarimetric Rate (deg min ⁻¹)	Initial Rate (mole liter ⁻¹ sec ⁻¹)	Relative Rate
A. Using 0.05M XVI and 1.25M Methanol in Benzene.				
0	-3.6	+0.0030	5.3 x 10 ⁻⁷	1.0
4.4M acetic acid	-3.5	+0.0014	2.6 x 10 ⁻⁷	0.5
0.25M triethylamine	-4.1	+0.352 ^a	5.50 x 10 ⁻⁵	103.8
0.25M 2,4,6-collidine	-3.5	+0.019 ^a	3.5 x 10 ⁻⁶	6.6
0.25M 2,6-lutidine	-3.8	+0.011	1.9 x 10 ⁻⁶	3.6
0.25M 2-picoline	-3.8	+0.012	2.1 x 10 ⁻⁶	4.0
0.25M pyridine	-3.8	+0.013	2.3 x 10 ⁻⁶	4.5
B. Using 0.082M XVI and 5.0M Methanol in Benzene.				
0	-5.9	+0.0278	4.9 x 10 ⁻⁶	1.0
0.74M CCl ₃ COOH ^b	-6.2	+0.0198	3.3 x 10 ⁻⁶	0.7

^a Taken from Figures 1 and 2.

^b The product isolated after a reaction time of 800 min is that reported in Section 4. (c) v of the Experimental.

TABLE V

The Influence of Methanol Concentration upon the Rate of the Reaction between Di-O-acetyl-2-nitro-D-xylal (XVI) and Methanol

<u>[Methanol]</u> (mole liter ⁻¹)	<u>Initial Polarimetric</u> <u>Rate</u> (deg min ⁻¹)	<u>Initial Rate</u> ^a (mole liter ⁻¹ sec ⁻¹)	<u>Relative</u> <u>Rate</u>
A. Using 0.082M XVI in Benzene ^a			
0	0	0	0
0.74	+0.0032	5.6×10^{-7}	0.11
1.85	+0.0112	2.0×10^{-6}	0.40
4.98	+0.0278	5.0×10^{-6}	1.00
B. Using 0.050M XVI in Benzene which is 1.25M in 2,4,6-Collidine ^a			
0	0	0	0
0.25	+0.0076	1.4×10^{-6}	0.20
0.63	+0.0202	3.6×10^{-6}	0.48
1.25	+0.0432	7.7×10^{-6}	1.00

^a The initial observed rotations were -5.9° and -3.5° in A and B, respectively.

TABLE VI

The Influence of the Alcohol Structure upon the Rate of its
Reaction with Di-O-acetyl-2-nitro-D-xylal (XVI)

<u>[Alcohol]</u> (mole liter ⁻¹)	<u>Initial Polarimetric</u> <u>Rate</u> (deg min ⁻¹)	<u>Initial Rate</u> (mole liter ⁻¹ sec ⁻¹)	<u>Relative</u> <u>Rate</u>
A. Using 0.082M XVI in Benzene ^a			
4.98 CH ₃ OH	+0.0278	4.9 x 10 ⁻⁶	1.00
4.95 CH ₃ CH ₂ OH	+0.0135 ^b	2.2 x 10 ⁻⁶	0.46
4.95 ØCH ₂ OH	+0.0101 ^b	1.8 x 10 ⁻⁶	0.38
B. Using 0.050M XVI and 0.76M 2,4,6-collidine in Benzene ^a			
1.18 p-O ₂ N-Ø-CH ₂ OH	+0.054 ^c	9.2 x 10 ⁻⁶	1.59
1.22 p-CH ₃ O-Ø-CH ₂ OH	+0.042 ^c	7.2 x 10 ⁻⁶	1.24
2.02 ClCH ₂ CH ₂ OH	+0.039 ^c	6.6 x 10 ⁻⁶	1.14
1.25 CH ₃ OH	+0.0338	5.8 x 10 ⁻⁶	1.00
1.22 ØCH ₂ OH	+0.033 ^c	5.7 x 10 ⁻⁶	0.98
1.29 CH ₃ CH ₂ OH	+0.0122 ^c	2.1 x 10 ⁻⁶	0.36
1.25 Ø ₂ CHOH	+0.0017 ^c	2.9 x 10 ⁻⁷	0.050
1.28 (CH ₃) ₂ CHOH	+0.0013 ^c	2.2 x 10 ⁻⁷	0.038

^a The initial observed rotations were -5.9° and -3.9° for A and B, respectively.

^b The initial polarimetric rate was found for a 4.98M solution of ROH by calculation assuming a reaction first order in ROH.

^c The initial polarimetric rate was calculated for a solution 1.25M in ROH and 0.76M in 2,4,6-collidine by assuming the reaction is first order in ROH and using Fig. 1 to allow for the change in the concentration of the 2,4,6-collidine.

iv) Effect of alcohol structure (basic conditions). - Compound XVI (24.5 mg, 0.100 mmole) was weighed into the 2.0 ml graduated flask and 2,4,6-collidine (200 μ l, 1.52 mmole) was injected. Its weight was found by difference. This mixture was then dissolved in approximately 0.5 ml benzene. Then the alcohol (approx. 2.5 mmole), which had been weighed out separately in another flask, was transferred together with benzene washings to the graduated flask. The volume of reaction mixture was adjusted to the standard mark with benzene. The results are presented in Table VI.

(e) Influence of Tetrahydrofuran in the Presence
of Base

Compound XVI (24.5 mg, 0.100 mmole) was weighed into the 2.0 ml volumetric flask and dissolved in tetrahydrofuran (approx. 0.5 ml). After addition of the previously described 5M methanol in benzene solution (0.50 ml) and the previously described triethylamine in benzene solution (0.30 ml), the volume of the reaction mixture was adjusted to the standard mark with tetrahydrofuran.

The same procedure was adopted when 2-propanol was the alcohol, except that the 2-propanol was weighed with XVI before dissolution of the mixture in tetrahydrofuran. (The uncatalysed reaction of XVI with 2-propanol is very slow). For comparison purposes, an identical reaction was performed except that benzene replaced the tetrahydrofuran. The results are presented in Table VII.

TABLE VII

The Influence of Tetrahydrofuran upon the Triethylamine-catalysed Reactions of Di-O-acetyl-2-nitro-D-xylal (XVI) with Alcohols

<u>[Alcohol]</u> (mole liter ⁻¹)	<u>Solvent</u> (v/v)	<u>Initial</u> <u>Polarimetric</u> <u>Rate</u> (deg min ⁻¹) _a	<u>Initial</u> <u>Rate</u> (mole liter ⁻¹ sec ⁻¹) _c	<u>Relative</u> <u>Rate</u>
1.25 CH ₃ OH	Benzene	+0.280	5.0 x 10 ⁻⁵	1.00
1.25 CH ₃ OH	63% THF ^b 37% benzene	+0.0695	1.2 x 10 ⁻⁵	0.24
1.19 (CH ₃) ₂ CHOH	Benzene	+0.005	8 x 10 ⁻⁷	1.0
1.16 (CH ₃) ₂ CHOH	85% THF ^b 15% benzene	+0.003	5 x 10 ⁻⁷	0.6

a The initial polarimetric rate is reported for benzene solutions that are 0.050M in XVI and 1.25M in triethylamine. Calculations were made to adjust [(CH₃)₂CHOH] to 1.25M on a first-order basis.

b Tetrahydrofuran.

c The initial observed rotations were -3.7° and -4.1° when tetrahydrofuran was present and absent, respectively.

5. Reaction of 3,4-Di-O-acetyl-2-nitro-D-xylal (XVI)
with Methanol and Subsequent Reactions.

(a) Reaction Conditions and Sampling Technique

In all reactions, a 1.584% w/v (0.0648M) solution of XVI was reacted in 75% methanol - 25% benzene at 26°. XVI was weighed into the dry volumetric flask and placed in vacuo to remove traces of atmospheric moisture adsorbed during the weighing process. It was then dissolved, with warming, in the measured volume of dry benzene. The flask was cooled to room temperature and dry methanol added to adjust the total volume to the standard mark. This procedure allowed the reaction to be followed shortly after it had started. The necessary kinetic conditions could not be obtained with pure methanol as solvent since XVI dissolved only slowly in methanol at 26°.

While methanol was being added, the chart drive of a recording spectropolarimeter was started. After the 5 cm or 10 cm polarimeter tube had been filled with the reaction mixture and placed in the instrument, the recorder was started. At suitable periods, samples were removed, the solvent quickly evaporated at 30° in a rotatory evaporator, the syrup dissolved in benzene and the solution again concentrated, and this procedure repeated. Then the syrup was dissolved in dry carbon tetrachloride and the solution concentrated. This procedure was repeated and the remaining syrup placed in vacuo at 50° for twenty minutes.

This isolation procedure was found to leave the compounds found in the reaction sequence intact, and was used to remove most, or all, of the acetic acid produced in the initial reaction. The rotary evaporator that was used permitted reaction samples to be concentrated to a syrup within one or two minutes without undue warming of the sample. Evaporation of the solvent at a bath temperature of 30° reduced the sample temperature considerably since the flask always remained cold to the touch during evaporation. In summary, the isolation procedure was rapid and did not involve heating or decomposition of the sample.

Five runs were performed as described and, in view of the discrepancies observed (Table XVI), three further runs were made to determine the effect of impurities. All three experiments were performed with portions of the same sample of XVI except that in the eighth run the sample was left in the atmosphere for ten minutes. Previous experiments had shown XVI to be hygroscopic. In the sixth and eighth runs, the benzene, which was dried by standing over sodium wire, was used directly. The seventh run was performed under the same conditions as Runs one to five.

The sample (77 mg) from Run 2b (Table XVI) was free of acetic acid (P.M.R.). It was dissolved in 1.2 ml of benzene and the solution diluted to 5 ml with methanol. Since the sample had originally been a 5 ml aliquot of reaction mixture, the concentrations of the reactants in this new reaction mixture were the same as before. After 25.5 hr of polarimetric monitoring, this reaction mixture was worked up as usual.

(b) Sample Evaluation

All samples were examined as deuteriochloroform solutions by P.M.R. spectroscopy at 60 Mc.p.s. The deuteriochloroform was exchanged for chloroform by successive evaporations and the I.R. spectra determined on 10% w/v chloroform solutions. These solutions were then concentrated and the products stored in stoppered flasks at 0° in the dark. The reaction times and rotations and the sample compositions are reported in Table XVI. The sample compositions were determined from the integrations of the P.M.R. spectra of the samples. After integration of the whole spectrum, the peaks downfield from the methoxy signals were integrated at a greater amplitude. In every case, the two integrals were comparable to within a few per cent after the ratio of the products (spectrum current multiplied by integral current) had been taken into consideration.

The non-olefinic products (XXVI and XXVII) were readily detected by their strong absorptions in the I.R. spectra (Table XV) at 1560 and 1563 cm^{-1} , respectively. By comparison, compounds XVI, XXIV and XXV absorbed strongly at 1509, 1538 and 1511 cm^{-1} , respectively. The appearance of XXVII was clearly indicated by its signal for methoxy at τ 6.54 in the P.M.R. spectrum. As seen in Table XIV, the signals for H_1 of the compounds XVI, XXIV and XXV were easily distinguished. The relative amounts of these compounds were given by the relative intensities of these signals and were checked by reference to other signals; for example, H_3 of XVI and XXIV. The intensity of the signals for methoxy

group in conjunction with the signals for H_1 of XXIV and XXV could then be used to estimate the amount of XXVI except where appreciable amounts of XXVII were present. In the latter case, estimation of the relative amounts of XXVI and XXVII present was more difficult and less accurate. After allowing for the olefinic products, the integral of the τ 6.3 to 6.8 region provided the relative intensity of the total non-olefinic products. The ratio of the amounts of XXVI and XXVII was given, albeit approximately, by comparison of the peak-heights of the methoxy signals at τ 6.54 (XXVII - one methoxy) and τ 6.50 (XXVI and XXVII - one methoxy each).

In this manner, the sample from Run 2b that was further reacted for 25.5 hr was found to contain compounds XXIV, XXV, XXVI and XXVII in 7, 26, 59 - 67 and 0 - 8 mole %, respectively.

An attempt was made to evaluate the samples by gas-liquid partition chromatography. Column A (10% Apiezon M on Chromosorb W, 6 feet by 1/8 inch i.d.) gave well defined peaks for all eluted compounds. Although compounds XVI, XXIV and XXV were separated, no separation of XXV, XXVI and XXVII was observed. Column B (5% diethylene glycol adipate, 3% GE SE52 on Chromosorb W, 8 feet by 1/8 inch i.d.) allowed the separations which are described below.

The samples used were 20 μ l portions of 10% methylene chloride solutions. The best separations of the constituents of the sample from Run 3a (Table XVI) were made with a helium flow of 80 ml per min and a temperature programme that started at 140°C and rose at 3° per min. Two peaks were

produced at retention times of about 15 min with a peak to peak separation of 1.3 min. Admixture of some XVI with the sample increased the second peak showing it to be due to XVI. The eluate corresponding to the first peak was collected on the previously described multiple internal reflectance cell fitted with a solid state cooling device. The whole collection apparatus was enclosed in a plastic bag containing calcium chloride dessicant to avoid condensation of atmospheric moisture. The I.R. spectrum of the collected material was that for XXIV.

Attempts to chromatograph compounds XXVI and XXVII showed no peaks attributable to compounds other than XXV. In the case of XXVII, when column B was used with a helium flow rate of 110 ml per min and a temperature programme that started at 170°C and rose at 1.1°C per min, the only product eluted was XXV with a retention time of 10 min. The material was identified by I.R. spectroscopy as described above for XXIV.

(c) Isolation and Characterisation of Methyl 4-O-acetyl-2,3-dideoxy-2-nitro-β-D-glycero-pent-2-enopyranoside (XXIV)

i) Isolation. - The sample from Run 1a, which was rich in XXIV, crystallised after several months storage to provide seed crystals, m.p. 103.5 - 105°.

Compound XVI (792 mg) was dissolved in dry benzene (12 ml) and the volume of the solution adjusted to 50.0 ml with dry methanol. This solution was then used to fill a

10 cm polarimeter tube. After 105 min, when the observed rotation had reached $+0.03^\circ$, the entire solution was worked up in the usual fashion, yielding 780 mg of a pale yellow syrup. When seeded, the syrup rapidly crystallised as long colorless needles. The product was recrystallised from di-isopropyl ether, and the first two crops were combined to give 323 mg of crystals with m.p. $104.5 - 106^\circ$ and $[\alpha]_D^{27} +102^\circ$ (c , 1 in chloroform).

Anal. Calcd. for $C_8H_{11}NO_6$: C, 44.24; H, 5.11; N, 6.45%, M.W., 217.2. Found: C, 44.36; H, 5.14; N, 6.43%; M.W., 230.

The yield was 46%. The P.M.R. spectrum is reproduced in Fig. 35 and the parameters recorded in Table XIV.

ii) Hydrogenation. - Compound XXIV (79 mg) was hydrogenated at atmospheric pressure in ethyl acetate (15 ml) over 5% palladium - charcoal (~50mg, A.D. MacKay, Inc.) and absorbed four equivalents of hydrogen during fifteen hours. The catalyst was removed by filtration through a bed of Celite supported on a sintered glass funnel and the ethyl acetate solution concentrated in vacuo at 50° . The remaining syrup was treated with acetic anhydride (5 ml) and anhydrous sodium acetate (~50 mg) at 100° for 30 min. The acetic anhydride was removed by concentration of the solution followed by two evaporations of m-xylene from the residue. The product was dissolved in chloroform (10 ml) and water (5 ml), the aqueous layer extracted with chloroform and then the combined chloroform layers dried over anhydrous calcium chloride. The dessicant was removed by filtration, and the solution concentrated in vacuo to yield 84 mg of a yellow syrup. The P.M.R. spectrum of this product showed the ratio of acetoxy to methoxy signals could be two to one. However, at

least six acetyl signals were evident and strong absorptions were present in the region τ 8.5 to 9.2. The sample was therefore a mixture of several compounds and was not investigated further.

iii) Configuration of the anomeric centre. - Compound XXIV (22 mg)

was dissolved in dry benzene (0.4 ml), dry triethylamine (10 μ l, 0.07 mmole) added, and then the volume of this solution adjusted to 2.0 ml with dry ethanol. This solution was used to fill a 5 cm polarimeter tube and the rotation was followed until a constant value was reached. The observed rotation (deg) and time (min) were: +1.07, zero time; +0.98, 10; +0.80, 30; +0.64, 50; +0.23, 120; +0.11, 150; -0.47 (final), 550. The reaction mixture was concentrated to give 25 mg of a pale yellow syrup. The P.M.R. spectrum (Fig. 15) of this product, XXVIII, showed the acetoxy, ethoxy and methoxy functions to be present in equal ratios. The coupling constants (c.p.s.) were: $J_{1,2}$, 7.7; $J_{2,3}$, 10.0; $J_{3,4}$, 9.0; $J_{4,5e}$, 5.6; $J_{4,5a}$, 9.9; $J_{5a,5e}$, 11.9; and τ values were: H_1 , 5.32; H_2 , 5.60; H_3 , 5.92; H_4 , 5.13; H_{5e} , 5.87; H_{5a} , 6.72; OCH_3 , 6.54; OAc , 7.92. The ethyl signal appeared to be an ABX_3 system with CH_3 at τ 8.90 and CH_2 as a multiplet centered at about τ 6.45. The signals were attributed to methyl 4-O-acetyl-2-deoxy-3-O-ethyl-2-nitro- β -D-xylopyranoside XXVIII. Attempts to crystallise this product failed.

(d) The Characterisation of 4-O-acetyl-3-O-methyl-2-nitro-D-xylal (XXV)

Trial T.L.C. on silica gel G showed compounds XVI, XXIV and XXV to be fairly well separated with di-isopropyl ether as the eluant. However, the two non-olefinic products XXVI and

XXVII had similar R_f values to those of XXIV and XXV. A 32 x 2.8 cm column was prepared from a slurry of dry silicic acid (85 g, Mallinckrodt 100 Mesh) in di-isopropyl ether. The combined isolated reaction samples from Runs 3c, 5a, 5b, 6a, 7 and 8 (630 mg) were placed on the column as a saturated di-isopropyl ether solution. Fractions (2 ml) were collected every 15 min, and after removing the solvent by subjecting the solution to a compressed air jet, chloroform (2.0 ml) was added and the rotation of these solutions taken in a 10 cm polarimeter tube. Collection tube numbers and observed rotations (deg) were: 1 to 96, 0.000; 97, +0.087; 98, +0.047; 99, -0.095; 100, -0.210; 102, -0.331; 104, -0.555; 106, -0.638; 110, -0.875 (minimum); 115, -0.840; 125, -0.453; tailing to tube 186. These rotations indicated a partially resolved mixture of XXIV and XXV and this was confirmed by T.L.C. examination of tubes at suitable intervals. The eluate between tubes 120 and 130 had the maximum relative concentration of XXV, and the P.M.R. spectrum of this fraction (a syrup, weight 61 mg) indicated 85% XXV, the remainder being XXIV and XXVI present in equal amounts. This mixture had $[\alpha]_D^{27} -122^\circ$ (\underline{c} , 2.4 in chloroform). Attempts to increase the concentration of XXV in this fraction by distillation in vacuo at 100° failed and gave darkening and apparent decomposition of the sample. Compound XXV was characterised by its P.M.R. (Fig. 38) and I.R. spectra. These are reported in Tables XIV and XV in section 4 of the Discussion.

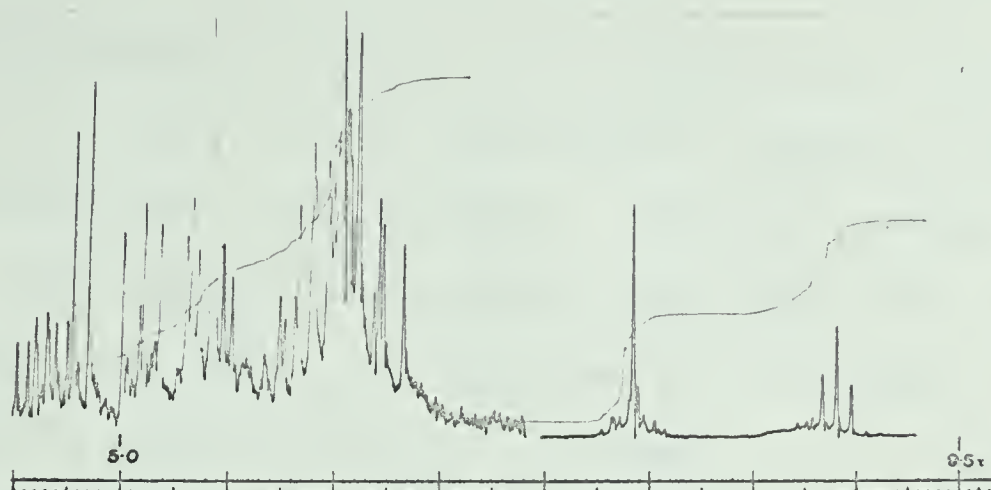


FIG. 15. P.M.R. spectrum (100 Mc.p.s.) of the product from ethanol and triethylamine treatment of compound XXIV. Acetoxy and ethyl $-CH_3$ signals are at reduced amplitude. EXPERIMENTAL, Section 5. (c)iii).

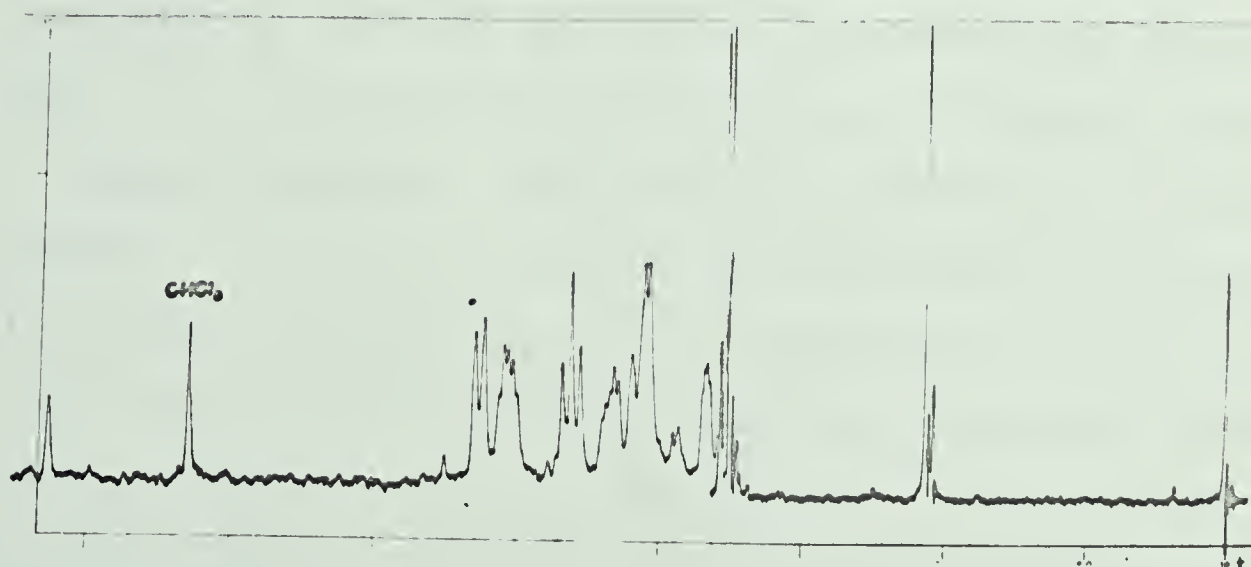


FIG. 16. P.M.R. spectrum (60 Mc.p.s.) of the sample from the reaction of XVI with methanol (Run 2d, reaction time 46.8 hr). EXPERIMENTAL, Section 5. (e) i).

(e) The Characterisation of Methyl 4-O-acetyl-2-deoxy-
3-O-methyl-2-nitro- β -D-lyxopyranoside (XXVI)

i) Preparation of XXVI. - The compound could not be obtained in the pure state and was consequently studied in admixture with compounds XXIV, XXV and XXVII. This was possible since products from the kinetic investigation (see Table XVI) contained up to 75 mole % of XXVI. The spectrum of the sample isolated from Run 2d is given in Fig 16. The peak at τ 2.7 was due to chloroform. The peaks at τ 1.73 and τ 4.49 could be assigned to the presence of compounds XXV (15%) and XXIV (5%), respectively. The chemical shift and intensity of the acetyl peak at τ 7.93 allowed its assignment to XXV. The relative intensities of the acetyl (τ 7.87) and methoxy signals (τ 6.4 - 6.5) and the nitrogen content of the mixture, 5.4% (expected 5.7%), together with the strong absorption in the I.R. at 1560 cm^{-1} required the main component (XXVI, 70 - 75%) to be a mono-O-acetyl-di-O-methyl derivative of a deoxynitropentose (see below for reduction to amine). The doublet at τ 4.72 was collapsed by simultaneous irradiation of the triplet centered at τ 5.38. Irradiation in the region of τ 5.8 - 6.0 collapsed both the multiplet centered at about τ 4.93 and the triplet at τ 5.38. On this basis, and in view of both the coupling interactions and chemical shifts, XXVI must be a methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro-pentopyranoside. Its configuration was established as β -D-lyxo on the basis of the following epimerisation reaction. Its conformation is examined in the Discussion.

ii) The reductions of impure XXVI. - A magnetically stirred slurry of 5% palladium - charcoal (50 mg) in ethyl acetate (5 ml) and concentrated hydrochloric acid (20 μ l, 0.2 mmole) was hydrogenated at 0° at atmospheric pressure. Then the isolated reaction sample from Run 2d (41 mg) which contained 70 - 75 mole % XXVI, was injected as a solution in ethyl acetate (3 ml). Hydrogen uptake was observed and allowed to continue 15 hr before removal of the catalyst by centrifugation and filtration. Concentration of the remaining solution gave 40 mg of a syrup, a small portion of which gave a positive test when warmed with ninhydrin reagent solution (107). After dissolution in tetrahydrofuran and deuterium oxide, the resulting solution was freeze-dried, and then this process repeated. The P.M.R. spectrum at 100 Mc.p.s. (Fig. 17) in acetone- d_6 showed that the major constituent of this sample was not XXVI. It had a multiplet (two protons) at τ 4.9, a second multiplet (two protons) at τ 5.9, and a third multiplet coincident with the two OCH_3 signals. In addition, there was one acetoxy signal. Spin-spin decoupling revealed $J_{3,4} \approx J_{4,5a} \approx 6$ c.p.s., $J_{4,5e} = 3.8$ c.p.s., and $J_{5a,5e} = 12.0$ c.p.s. Using this technique, the following signals could be assigned: H_4 , τ 4.80; H_{5e} , τ 5.88; H_3 and H_{5a} , τ 6.5. However, no assignment could be made for H_1 and H_2 other than that they were at τ 4.9 and τ 5.9. Addition of pyridine produced insignificant chemical shift changes compared to the previously described spectrum and, unfortunately, led to decomposition of the sample on storage.

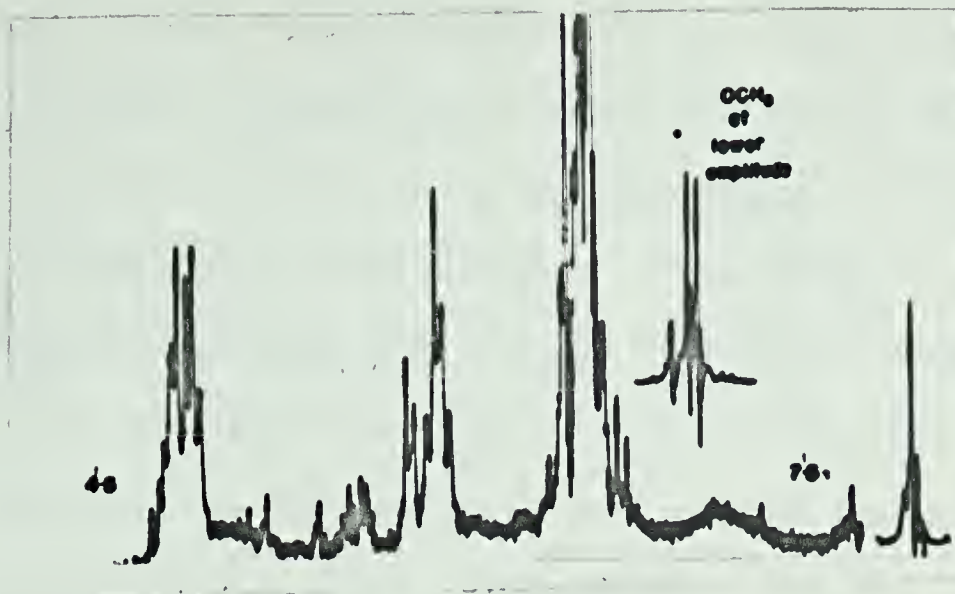


FIG. 17. P.M.R. spectrum in acetone-d₆ (100 Mc.p.s.) of the product from catalytic hydrogenation of the sample from Run 2d (Fig. 16) which contained 70-75 mole % XXVI. (Acetoxy at reduced amplitude), EXPERIMENTAL, Section 5. (e) ii).

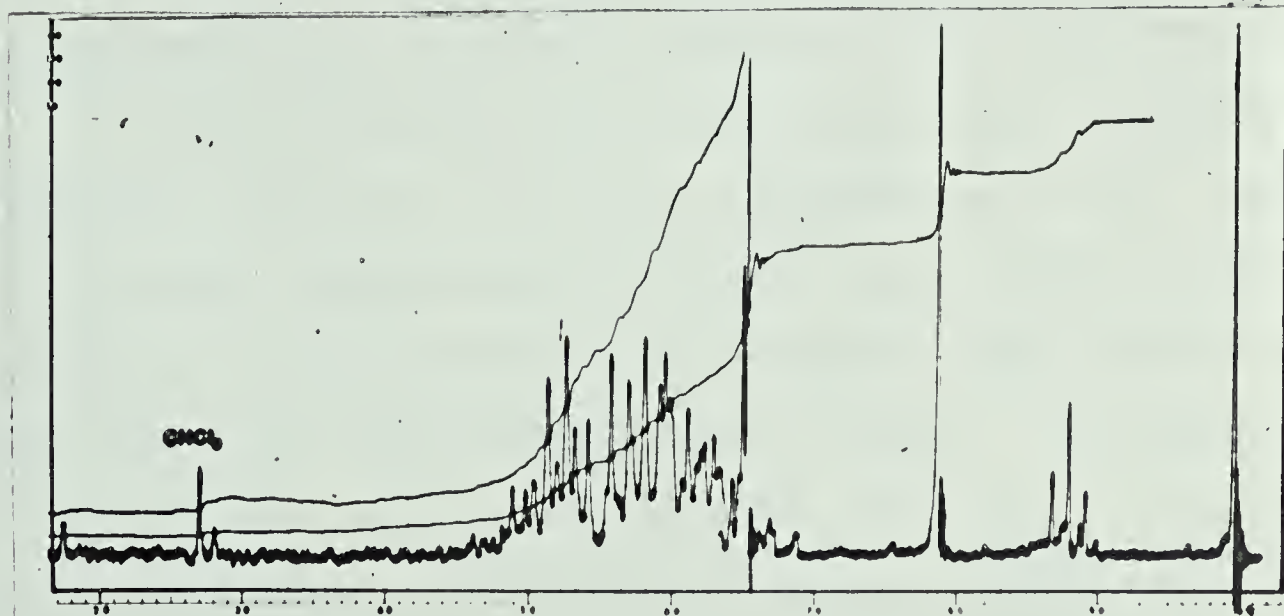


FIG. 18. P.M.R. spectrum (60 Mc.p.s.) of the product from ethanol and triethylamine treatment of the sample from Run 2c which contained 65 mole % XXVI. EXPERIMENTAL, Section 5. (e) iii).

The sample from Run 4b (77 mg) was hydrogenated with Adam's catalyst in methanol containing excess concentrated hydrochloric acid. The product (69 mg) was exchanged with deuterium oxide as previously described and examined as an acetone- d_6 solution by P.M.R. spectroscopy. The spectrum was similar to that found previously. This product was deacetylated by treatment with methanol (10 ml) and conc. hydrochloric acid (0.15 ml) at 60° for two hours. P.M.R. spectroscopy confirmed that deacetylation had occurred and showed the presence of a multiplet with intensity \leq one proton at $\tau 4.8$. T.L.C. on microcrystalline cellulose (108) with butanol-pyridine-acetic acid-water (6:4:3:1) revealed three separated spots. A minor spot had the same color (dark blue) and chromatographic mobility ($R_{gm} \sim 5$) as the deacetylated reduction product of XXVII (EXPERIMENTAL, Section 6c). Glucosamine hydrochloride was the standard with $R_{gm} = 1.0$, and ninhydrin (107) the developing agent.

The aglycones in both mixture and this standard were removed by refluxing 15 hr with N hydrochloric acid, and the mixture again examined with the same T.L.C. system with glucosamine hydrochloride as the standard. The mixture gave three spots with the ninhydrin spray reagent. The major spot had $R_{gm} \sim 6$ (dark blue), and two minor spots $R_{gm} \sim 3$ (maroon) and $R_{gm} \sim 2$ (dark blue). The similarly derived product from XXVII gave a maroon-colored spot at $R_{gm} \sim 3$ identical with one of the minor spots of the mixture.

iii) The "epimerisation" of XXVI in ethanol and triethylamine. -

The sample from Run 2c (9% XXIV, 26% XXV, 65% XXVI and a trace of XXVII) had a P.M.R. spectrum (Fig. 39) very similar to that

of Run 2d. The material was dissolved in benzene (1.0 ml) and triethylamine (30 μ l, 0.2 mmole) and then ethanol (4.0 ml) added. This solution was used to fill a 5 cm polarimeter tube, and the rotation was monitored continuously. The observed rotations (deg) and times (min) were: -0.45, zero time; -0.41, 50; -0.39, 100; -0.36, 200; -0.33, 400; -0.31, 800; -0.30, 1000. At this latter time, it was concentrated to a syrup and then toluene and carbon tetrachloride were each twice evaporated from the residue. The P.M.R. spectrum is reproduced in Fig. 18 and discussed in detail in Section 4 of the Discussion. It will be seen that the product is a mixture of about 6:3:1 of ethyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-xyloside (XXIX), the corresponding methyl glycoside (XXVII) and methyl 4-O-acetyl-2-deoxy-3-O-ethyl-2-nitro- β -D-xyloside (XXVIII), respectively.

The only observable effect of treating impure XXVI with 2,4,6-collidine in deuteriochloroform at room temperature was the formation of XXV.

(f) The Characterisation of Methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-xylopyranoside (XXVII).

The syrupy samples from several prolonged reaction runs deposited crystals on storage. That this crystalline material was XXVII was shown by the m.p. 124-5°, undepressed on admixture with XXVII prepared in a base-catalysed reaction of XVI with methanol (EXPERIMENTAL, Section 6) and by I.R. spectroscopy. The samples that provided the seed crystals were known (P.M.R.) to contain significant quantities of XXVII.

6. The Reaction of 3,4-Di-O-acetyl-2-nitro-D-xylal (XVI)
with Methanol in the Presence of Tertiary Amines.

(a) Under Continuous P.M.R. Spectroscopic Observation

Compound XVI (75 mg, 0.30 mmole) was dissolved in deuteriochloroform (approximately 0.4 ml) and a drop of TMS added for internal reference. After recording the spectrum, dry methanol (80 μ l, 2.0 mmole) was injected into the sample tube and the spectrum recorded for a period of ten minutes during which no observable amount of XXIV was formed. Dry triethylamine (42 μ l, 0.30 mmole) was injected and the P.M.R. spectrum immediately recorded. The reactions were seen to proceed rapidly, and at five minutes, three C-OCH₃ signals were visible. At the stated times (min), the concentrations (%) were:

XVI: 1/4, 80; 4, 20; 6, 3; 13, 0.

XXIV: 0, 0; 1, 30-40; 3, 50-60; 7, 30-40; 14, 15-20; 20, 8-10.

XXVII: 4, 40; 9, 75; 16, 85; 22, ~100.

Small peaks were present in the region τ 1.7 - 1.9 at 6 min and thereafter. Integration of the spectrum showed that one equivalent of acetic acid or acetate ion (sharp, high-field acetoxy signal) was present at 22 min. After 42 hr, the spectrum indicated that a mixture was present that consisted mainly of XXVII together with minor amounts of other products. These were possibly some α -anomer of XXVII, and either XXV or a reaction product of XXV with triethylamine.

(b) The Preparation of XXVII

Compound XVI (388 mg, 1.58 mmole) was weighed into a flask and placed in vacuo to remove adsorbed moisture. After dissolution in 6 ml of dry benzene, 0.50 ml (3.5 mmole) of dry triethylamine was added and the solution diluted to 25 ml with dry methanol. This solution was used to fill a 5 cm polarimeter tube. The reaction time (min) and observed rotation (deg) were: zero time, approx. -2.6; 10, -0.8; 30, 0.0; 50, +0.2; 90, +0.1; 150, -0.1; 250, -0.32; 400, -0.37; 600, -0.38. After constant rotation had been reached (600 min), the solution was concentrated at 35°. Excess triethylamine was removed by dissolving the syrup in chloroform, and re-concentrating, and then repeating this process. Then the remaining syrup was dissolved in chloroform, the solution washed with half its volume of N hydrochloric acid, and with a little water. The aqueous washings were twice extracted with chloroform, then all the chloroform portions combined, dried over anhydrous sodium sulfate, and concentrated. The product, 331 mg of a yellow oil, quickly crystallised on storage. The P.M.R. spectrum showed that both the crude reaction product and the crystalline material were essentially pure XXVII. The analytical sample of XXVII, 258 mg (65% yield), was obtained by sublimation on a steam bath at approximately 0.3 mm pressure. XXVII had m.p. 124 - 125°, unchanged on admixture with seed crystals isolated from uncatalysed runs, and $[\alpha]_D^{27} -37^\circ$ (c, 1 in chloroform). The P.M.R. spectrum is reproduced in Fig. 33.

Anal. Calcd. for $C_9H_{15}NO_7$: C, 43.37; H, 6.07; N, 5.62%; M.W., 249.2. Found: C, 43.30; H, 5.76; N, 5.69%; M.W., 278.

The residue from the sublimation was semi-crystalline and its P.M.R. spectrum showed it to be a mixture of XXV and XXVII.

When the reaction mixture was allowed to stand several days, the rotation underwent a very slow dextrorotatory change.

Similar results were obtained with 2,4,6-collidine or pyridine as catalysts, although the reactions were considerably slower.

(c) The Hydrogenation of XXVII

Compound XXVII (76 mg) was injected as a methanol solution (3 ml) into a prehydrogenated slurry of Adam's catalyst (~50 mg) in methanol (20 ml) containing concentrated hydrochloric acid (100 μ l, 1 mmole) at 23°. The uptake of hydrogen was slow and effectively ceased after 12 hr at which time approx. 2 mole equivalents had been absorbed. After removal of the catalyst by filtration, the methanol solution was concentrated to give a yellow syrup, the P.M.R. spectrum of which indicated partial deacetylation. This product was treated with methanol (10 ml) and concentrated hydrochloric acid at 60° for 2 hr, and after concentration to a dark brown syrup (81 mg), the P.M.R. spectrum in acetone- d_6 showed little, if any, acetoxy groups to be left. This product gave a positive test with ninhydrin reagent, and T.L.C. on microcrystalline cellulose (108) gave one dark-blue spot with ninhydrin detection. The chromatographic mobility of this compound relative to those obtained in the hydrogenation of crude XXVI was reported earlier, as was the product of hydrolysis to 2-amino-2-deoxy-3-O-methyl pentose.

7. The Reaction of 3,4,6-Tri-O-acetyl-2-nitro-D-glucal (XIII) with Methanol.

(a) Conditions, Sampling and Evaluation of Samples

So that these results could be directly compared with those of the reaction between 3,4 -di-O-acetyl-2-nitro-D-xylal (XVI) and methanol, these reactions were performed under the same conditions of temperature, solvent etc., (Table VIII). A 2.06% w/v (0.0648M) solution of XIII was prepared in 75% methanol - 25% benzene as previously described for XVI (EXPERIMENTAL, section 5). The rotation of the reaction mixture was monitored continuously in a recording spectropolarimeter whose tube-holder was thermostatted at 26°. Aliquots were removed at suitable intervals and worked up as previously described.

Isolation procedures for samples of the triethylamine - catalysed reaction mixtures differed. Samples (usually about 5 ml) were withdrawn with a syringe and injected into a separatory funnel containing N hydrochloric acid (10 ml) and chloroform (10 ml), and then the whole mixture was vigorously shaken. After separation and removal of the chloroform layer, the latter was washed with N hydrochloric acid (5 ml). The aqueous layers were back-extracted, in turn, with chloroform (10 ml), and then the combined chloroform portions were dried over anhydrous sodium sulfate as before. The solution was decanted and, with chloroform washings of the dessicant, concentrated in vacuo in a tared flask. The residue was dissolved in toluene, reconcentrated and this process repeated once more with toluene, then

twice with dry carbon tetrachloride. The remaining syrup was kept at 50° at 0.3 mm for 30 minutes before examination by P.M.R. and I.R. spectroscopy as previously described for the XVI - methanol reaction. The I.R. and P.M.R. parameters are recorded in Tables XX and XXI. Satisfactory analyses could be made for the olefinic products, but not for the non-olefinic products, the prime cause being increased complexity of the P.M.R. spectra resulting from lack of stereospecificity of the reactions. Other isolation procedures in experiments in which the reaction of XIII with methanol was catalysed by triethylamine (Table IX) are described in section 7(c).

Some initial g.l.c. experiments were performed. This line of investigation was abandoned when it was found that no matter what programme, flow rate or column were used, XIII and its reaction products were only eluted at temperatures >200° as very broad and poorly defined peaks.

(b) Experimental Procedures

i) The uncatalysed reaction (Run 1). - Compound XIII (2.062 g, 6.48 mmole) was dissolved, with warming, in dry benzene (24 ml) in a 100 ml volumetric flask. Dry methanol was added to adjust the volume of the solution to the standard mark. This solution was used to fill a 10 cm polarimeter tube. The results are presented in Table XXII.

ii) Reaction catalysed by one equivalent of triethylamine (Run 2). - Compound XIII (515 mg, 1.62 mmole) was dissolved, with warming, in dry benzene (6.2 ml) in a 25 ml volumetric flask. Approximately 10 ml of dry methanol was added, followed

by dry triethylamine (226 μ l, 1.62 mmole), and then the volume of the reaction mixture was adjusted to the standard mark with dry methanol. The results are presented in Table XXIII.

iii) Reaction catalysed by 0.02 equivalent of triethylamine (Run 3). - The procedure described in the previous experiment was repeated, except in that a smaller volume of dry triethylamine (4.5 μ l, 0.032 mmole) was used. The results are presented in Table XXIII.

iv) Reaction of XIII with methanol (3.3M) in the presence of excess triethylamine (Run 4). - This reaction was performed to observe the effects of higher [triethylamine] and lower [CH₃OH]. Compound XIII (673 mg, 2.12 mmole) was dissolved in approximately 10 ml of dry benzene in a 25 ml volumetric flask. Methanol (3.37 ml, 83.5 mmole) and triethylamine (673 μ l, 4.8 mmole) were added and the volume of the reaction mixture adjusted to the standard mark with more benzene. This solution was used to fill a 5 cm polarimeter tube and the rotation of the reaction mixture recorded as before. The time (min) and observed rotation (deg) were: zero time, +0.20; 0.5, +0.26; 2.5, +0.50; 5, +0.62; 7, +0.65 (max.); 25, +0.50; 50, +0.38; 135, +0.35; 400, +0.30; 900, +0.28 (min); 4 days, +0.31; 7 days, +0.33; 12 days, +0.36. After concentration of the samples in vacuo at 30°, benzene and carbon tetrachloride were each twice evaporated from the residue in vacuo at 50°. Residual solvent was removed by keeping the product at 50° at 0.3 mm for 30 min for spectroscopic examination. The results are reported in Table XXIV.

TABLE VIII

Conditions for the Reaction of XIII with Methanol
at 26°

Run	[XIII] (M)	[Triethylamine] (M)	[Methanol] (M)
1	0.0648	0	~20
2	"	0.0648	~20
3	"	0.00128	~20
4	"	0.192	3.3

(c) The Final Products from the Triethylamine -
catalysed Reaction of XIII with Methanol

The reactions of several series of mixtures were taken to completion and then concentrated in vacuo at 30°. The reaction conditions and times are presented in Table IX. The remaining syrup was dissolved in benzene, the solution concentrated at 45°, then this process repeated once more with benzene and twice with carbon tetrachloride. This product was kept at 50° at 0.3 mm for 30 min and then these samples were examined by P.M.R. spectroscopy. In certain cases, the products were then deacetylated by warming with methanol (5 ml) and concentrated hydrochloric acid (0.3 ml). Then these solutions were concentrated in vacuo at 50°, dissolved in 98% ethanol and re-concentrated. This process was repeated twice more with 98% ethanol and once with carbon tetrachloride before examination of samples by P.M.R. spectroscopy as acetonitrile solutions. In this solvent, the hydroxyl group signals were generally

upfield from the methoxy signals and thus did not interfere with the analyses. The results are recorded in Table XXV.

i) The effect of changes in methanol concentration (Runs 5 - 8). -

Compound XIII (200 ± 5 mg, 0.63 ± 0.02 mmole) was dissolved in benzene and then methanol and triethylamine (0.20 ml, 1.4 mmole) were added. In run number 8, the triethylamine was added ten min prior to the addition of the methanol. The total volume in each run was approximately 7.2 ml.

ii) The effect of changes in triethylamine concentration

(Runs 9 - 13). - Compound XIII (100 ± 2 mg, 0.32 mmole) was dissolved in dry benzene (1 ml), then dry methanol (2.4 ml, 60 mmole) and triethylamine (13, 31, 44, 57 or 500 μ l) added. The total volume in each run was approximately 3.6 ml. The reaction mixture (run 9) containing the lowest concentration of triethylamine was monitored polarimetrically in a 5 cm tube. Reaction time (min) and observed rotation (deg) were: zero, +0.02; 10, +0.30; 25, +0.56; 50, +0.79; 100, +0.91, 200, +0.83; 500, +0.55; 1000, +0.39; 1500 plus, +0.35.

iii) The effect of changes in the concentration of XIII

(Runs 14, 15). - Dry methanol (48 ml) and triethylamine (620 μ l) were mixed and stored under anhydrous conditions. Then two separate samples of XIII (100 mg, 0.32 mmole) were dissolved in dry benzene (4.4 and 14.5 ml) and aliquots (10.5 and 35.0 ml, respectively) of the methanol - triethylamine mixture were added.

TABLE IX

The Triethylamine-catalysed Reaction of XIII with Methanol.

Run	[XIII]	[CH ₃ OH] (mole liter ⁻¹)	[Et ₃ N]	Reaction Time. (hr)
5	0.088	23.0	0.20	15
6	"	16.6	"	"
7	"	9.6	"	"
8 ^a	"	16.6	"	"
9	"	"	0.026	27
10	"	"	0.061	15
11	"	"	0.089	"
12	"	"	0.11	"
13	"	"	1.00	1
14	0.020	"	0.061	15
15	0.0061	"	"	"

^a The triethylamine was added 10 min prior to the addition of methanol.

(d) The Preparation of Methyl 4,6-Di-O-acetyl-2-deoxy-3-O-methyl-2-nitro-β-D-glucoside (XXXIII)

As indicated in the study of the effect of relative reactant concentration upon the final product composition, several equivalents of triethylamine had to be present for a high yield of XXXIII. Compound XIII (335 mg, 1.06 mmole) was

dissolved in approximately 5 ml methanol in a 10 ml volumetric flask. Triethylamine, (0.5 ml, 4 mmole) was added and the volume of the solution adjusted to the mark with more methanol. This solution was used to fill a 10 cm polarimeter tube. The time (min) and observed rotation (deg) were: 3, +0.6; 5, +1.1; 7, +1.5; 15, +1.3; 25, +1.0; 35, +0.9; 60 plus, +0.8. After three hr the solution and methanol washings were concentrated in vacuo at 30°. Carbon tetrachloride was evaporated twice from the brown oil, and the residue examined by P.M.R. spectroscopy which showed that XXXIII was the major carbohydrate constituent. This product was dissolved in chloroform (10 ml) and washed with N hydrochloric acid (10 ml), then water (5 ml). The aqueous layers were then back-extracted twice with chloroform (10 ml portions) and the combined chloroform portions dried over anhydrous sodium sulfate. Concentration in vacuo of this solution produced 297 mg of a yellow oil which crystallised on storage. Recrystallisation from n-hexane yielded 244 mg, (72%) of colorless needles with m.p. 114.5-116°, undepressed on admixture with crystals isolated from prolonged uncatalysed reactions, and $[\alpha]_D^{25} -5.2^\circ$ (c, 1.1 in chloroform). The P.M.R. spectrum is presented in Fig. 19.

Anal. Calcd. for $C_{12}H_{19}NO_9$: C, 44.86; H, 5.96; N, 4.36%; M.W., 321.3. Found: C, 44.56; H, 5.79; N, 4.27%; M.W., 322.

The P.M.R. spectrum of the product, XXXIII, was examined at 100 Mc.p.s. The chemical shifts (τ) were: H_1 , 5.24; H_2 , 5.51; H_3 , 5.93; H_4 , 4.97; H_5 , 6.28; H_6 , 5.72; H_6' , 5.88; OCH_3 , 6.48 and 6.58; OAc , 7.88 and 7.92. The coupling constants (c.p.s.) were: $J_{1,2}$, 8.1; $J_{2,3}$, 10.1*;

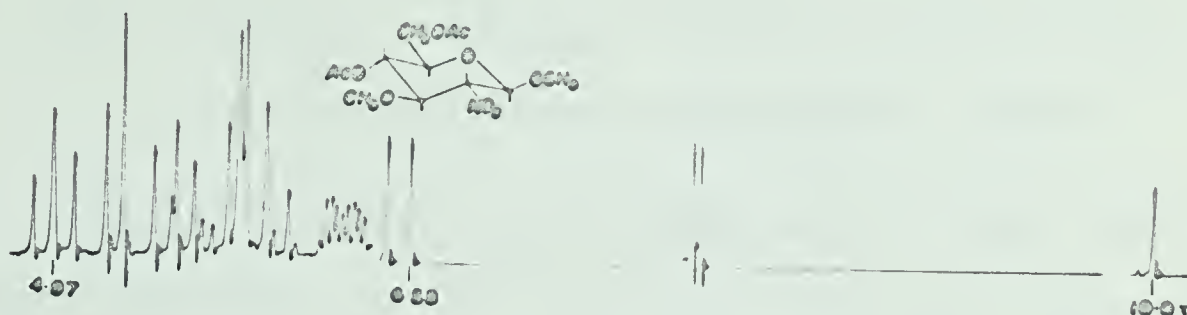


FIG. 19. P.M.R. spectrum (100 Mc.p.s.) of methyl 4,6-di-O-acetyl-2-deoxy-3-O-methyl-2-nitro-β-D-glucoside (XXXIII). EXPERIMENTAL, Section 7.(d).

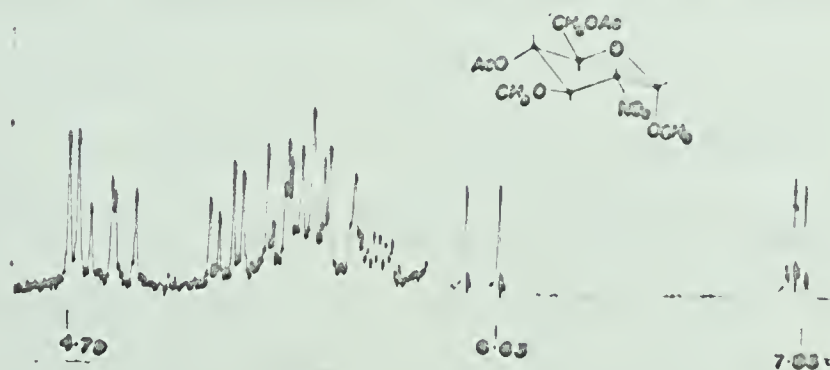


FIG. 20. P.M.R. spectrum (100 Mc.p.s.) of methyl 4,6-di-O-acetyl-2-deoxy-3-O-methyl-2-nitro-α-D-glucoside (XXXIV) EXPERIMENTAL, Section 7. (e).

$J_{3,4}$, 9.6*; $J_{4,5}$, 10.0*; $J_{5,6}$, 5.0*; $J_{5,6'}$, 3.1*; $J_{6,6'}$, 12.7.

The asterisk indicates coupling constants of which the assignments were demonstrated by spin-spin decoupling .

(e) Isolation of methyl 4,6-di-O-acetyl-2-deoxy-
3-O-methyl-2-nitro- α -D-glucoside (XXXIV)

Silicic acid (400 g, Mallinckrodt 100 Mesh) which had previously been dried at 250° for three days, was made into a slurry with 10% ethyl acetate in benzene (v/v) and this slurry used to form a column (48 x 4.6 cm) that was packed under a slight positive pressure. A syrupy mixture (4.903 g) containing mainly XXXIII and XXXIV was applied to this column as a concentrated solution in the same solvent. Then the column was eluted with this same solvent under a slight positive pressure. Fractions (~4.5 ml) were collected every 12 min and the rotation of every fifth fraction taken in a 10 cm polarimeter tube. After passage of ~600 ml solvent, a positive rotation was recorded for 35 fractions before the rotation became negative. These dextrorotatory fractions were examined by T.L.C. on silica gel G with 2% methanol in benzene (v/v) as the eluant. The first twenty fractions appeared to contain only a substance with $R_f \sim 0.55$ (cf. $R_f \sim 0.5$ for XXXIII). To avoid inclusion of any XXXIII, only the first ten fractions were used. These were combined and the solvent evaporated in vacuo at 30°. Carbon tetrachloride was twice evaporated from the remaining syrup before examination by P.M.R. spectroscopy.

The product (20 mg) was examined in the 100 Mc.p.s. P.M.R.

spectrometer with spin-spin decoupling and the spectrum is presented in Fig. 20. The chemical shifts (τ) were: H_1 , 4.81; H_2 , 5.46; H_3 , 5.73; H_4 , 4.98; H_5 , 6.07; H_6 and $H_{6'}$, 5.7 to 6.0; OCH_3 , 6.49 and 6.63; OAc , 7.89 and 7.93. The coupling constants were: $J_{1,2}$, 4.0*; $J_{2,3}$, 10.2; $J_{3,4}$, 9.0*; $J_{4,5}$, 10.3*; $J_{5,6}$ and $J_{5,6'}$, 2.7 and 5.4. The asterisk indicates a coupling constant of which the assignment was demonstrated by spin-spin decoupling. The recovered material, a syrup which failed to crystallise, had $[\alpha]_D^{27} + 107^\circ$ (c , 2.1 in chloroform). On the basis of the P.M.R. and polarimetric evidence, this compound (XXXIV) was identified as methyl 4,6-di-O-acetyl-2-deoxy-3-O-methyl-2-nitro- α -D-glucopyranoside.

(f) The Formation of 4,6-Di-O-acetyl-3-O-methyl-2-nitro-D-glucal (XIV) as a Reactive Intermediate

The P.M.R. spectrum of a sample from Run 1 (364 min reaction time, Table XXII) was examined at 60 Mc.p.s. to reveal singlets at τ 1.80 and τ 1.84. On adding 10 μ l of a 40% w/v solution of XIV in deuteriochloroform, the τ 1.80 signal increased in intensity relative to the other and this observation is taken as evidence for the presence of XIV in this reaction sample. The signal at τ 1.84 was then assumed to arise from H_1 of 4,6-di-O-acetyl-3-O-methyl-2-nitro-D-allal (XXXII).

(g) The Reaction of XIV with Methanol

i) Catalysed by triethylamine. - Compound XIV (75 mg, 0.26 mmole) was dissolved in approximately 0.5 ml dry benzene contained in a 2.0 ml volumetric flask. Dry triethylamine

(100 μ l, 0.7 mmole) was added and the volume of the reaction mixture adjusted to the standard mark with dry methanol. This solution was used to fill a 5 cm polarimeter tube. The time (min) and observed rotation (deg) were; zero time, + 1.18 ; 10, + 0.65; 25, + 0.44; 40, + 0.39, 70 plus, + 0.35. After 70 min , the solution was concentrated in vacuo at 30°, and carbon tetrachloride twice evaporated from the residue. Residual solvent was removed by keeping the product at 0.3 mm pressure at 50° for 30 min to leave 81 mg of a yellow crystalline material. Examination by P.M.R. spectroscopy indicated that the product was virtually pure XXXIII.

The reaction product was extracted with three 10 ml portions of warm diethyl ether. A crystalline material was deposited upon concentration of the extracts. This was recrystallised from n-hexane to give 49 mg of colorless clusters of needles with m.p. 114.5 - 116°, undepressed on admixture with XXXIII.

ii) Uncatalysed. - Compound XIV (46.4 mg, 0.16 mmole) was dissolved in benzene (1.2 ml) in a 5.0 ml volumetric flask. Then methanol was added to adjust the volume of the solution to the standard mark. This solution was used to fill a 5 cm polarimeter tube and the rotation recorded as described previously. The time (min) and observed rotation (deg) were: zero time, +0.28; 70, +0.26; 150, +0.24; 250, +0.23; 500, +0.22; 1000 plus, +0.21. After three days, the reaction mixture was concentrated in vacuo at 30° and carbon tetrachloride twice evaporated from the remaining syrup. Upon storage at 50° at

0.3 mm pressure for 30 min, 37 mg of semi-crystalline material was obtained. Examination by P.M.R. spectroscopy indicated the major constituent (~60%) to be XXXIII. Another di-O-acetyl-di-O-methyl substance, not XXXIV, was also present. Neither XIV nor XXXI were present.

8. The Reaction of 3,4,6-Tri-O-acetyl-2-nitro-D-glucal (XIII) and 4,6-Di-O-acetyl-3-O-methyl-2-nitro-D-glucal (XIV) with Tertiary Amines.

(a) Reaction of XIII with Tertiary Amines

Compound XIII (127 mg, 0.40 mmole) was dissolved in deuteriochloroform (0.4 ml) and the solution placed in a P.M.R. tube. The addition of triethylamine (35 μ l, 0.25 mmole) was accompanied by the slow formation of a brown-black coloration. The spectrum was recorded at suitable intervals and a new set of signals appeared. These were a singlet at τ 1.65, a doublet with a spacing of 4.0 c.p.s. at τ 3.6, and a quartet with spacings of 2.0 and 4.0 c.p.s. at τ 4.85. The intensities of these signals reached a maximum at about 30 min and then disappeared leaving no observable signals for any ring-protons. This result may be attributable to the presence of free radicals in the solution.

A similar set of signals was produced, although at a much slower rate, when 2,4,6-collidine was used.

Attempts to isolate a product gave only chloroform-insoluble intractable materials.

Compound XIII (110 mg, 0.35 mmole) was treated with triethylamine (35 μ l, 0.25 mmole) as above. After 13 min when

the signals of the intermediate were ~ 1.5 times as strong as those of XIII, methanol (100 μ l, 2.5 mmole) was added. These P.M.R. signals disappeared within four min of the addition, with those of XIII disappearing at a somewhat slower rate.

The reaction mixture was concentrated at 30° in vacuo, carbon tetrachloride twice evaporated from the brown oil remaining, and then the P.M.R. spectrum taken of the residue. The product was a mixture of several compounds. Integration showed that approximately 1.5 methoxy groups and 0.5 triethylamine groups were present for each molecule of compound.

(b) Reaction of XIV with Triethylamine

Compound XIV (77 mg, 0.27 mmole) was treated with triethylamine (34 μ l, 0.24 mmole) in a P.M.R. tube as above. The disappearance of XIV was ~ 160 times slower than that which had been observed for XIII, and no intermediate was observed. After eleven days, no signal for H_1 of XIV could be seen in the P.M.R. spectrum.

DISCUSSION

1. A P.M.R. Study of Glycal Conformations.

In the course of this research, the 100 Mc.p.s. P.M.R. spectra of the compounds listed in Table X were examined, and spin-spin (109) decoupling was used in certain cases to ensure the correct assignments. Decoupling was particularly useful in the case of long-range coupling. The P.M.R. parameters under specific conditions are presented in Table X.

The 3-O-acetyl-4,6-O-benzylidene derivatives of D-glucal (I) and D-allal (II) were examined as compounds of necessarily fixed conformation. It proved useful to develop a relationship between the dihedral angle (θ) defined by vicinal protons and the coupling constant (J). The 4,6-O-benzylidene glycals (I, II and III), by reason of the dioxan ring trans-fused to the flexible portion of the glycal ring, must have the dihedral angle between H_4 and H_5 ($\theta_{4,5}$) approximating to 180° . From Table X, it is seen that indeed $J_{4,5}$ values for these compounds are in the region 9.5 to 9.9 c.p.s. expected for vicinal, diaxially oriented protons (45, 46). 4,6-O-Benzylidene-D-allal (III) has coupling constants very similar to its 3-O-acetyl derivative. It is invariably found (46, 110, 111) that the coupling constant is virtually zero for protons that define a dihedral angle of 90° .

TABLE X

The Substituted Glycols Investigated by Proton Magnetic Resonance Spectroscopy.

Chemical Shifts τ^a (ppm),

H ₁	H ₂	H ₃	H ₄	H ₅	H _{6e}	H _{6a}	Acetate	Phenyl	Benzylidene	OH
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3-O-Acetyl-4,6-O-benzylidene-D-glucal^b (I)

3.96	5.28	4.31	6.08	6.30	5.92	6.56	8.35	2.4 to 3.0	4.73	—
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3-O-Acetyl-4,6-O-benzylidene-D-allal (II)

3.36	5.04	4.60	5.90	5.85	5.59	6.23	7.95	2.2 to 2.5	4.45	—
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4,6-O-Benzylidene-D-allal (III)

3.56	5.08	5.85	6.27	5.86	5.61	6.27	—	2.4 to 2.9	4.54	7.43
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3,4-di-O-acetyl-L-rhamnal (IV)

3.56	5.22	4.66	4.98	5.86	CH ₃	8.70	7.92, 7.96	—	—	—
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Coupling Constants τ^a (c.p.s.)

	J _{1,2}	J _{2,3}	J _{3,4}	J _{4,5}	J _{5,6e}	J _{5,6a}	J _{6e,6a}	J _{1,3}	J _{2,4}	J _{3,5}	J _{1,5}
I ^b	6.1	2.2 ^c	6.8 ^c	~9.5	3.8	9.8	9.1	1.5	~0 ^c	<0.4 ^c	~0.3 ^c
II	5.9 ^c	5.9 ^c	3.8 ^c	9.8	4.6	9.6	9.8 ^c	0.5 ^c	~0	~0	0.5 ^c
III	6.2 ^c	6.0 ^c	3.8 ^c	9.9 ^c	5.0 ^c	10.0 ^c	10.0 ^c	0.5 ^c	~0	~0	0.5 ^c
IV	6.3 ^c	3.2	6.3	8.5 ^c	J _{5,CH₃}	6.8.		1.6 ^c	0.5	0.9	<0.4 ^c

^a τ -Values and coupling constants measured at 100 Mc.p.s. with 20% w/v CDCl₃ solutions at 35°, unless otherwise stated.^b In benzene-d₆, see discussion.^c Demonstrated by double irradiation.

(—Cont'd —)

TABLE X (Cont'd).

Chemical Shifts^a (τ).

H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H _{6'}	Acetate	OCH ₃
3,4,6-Tri-Q-acetyl-D-galactal (V).								
3.54	5.27	4.44	4.57	(5.6 to 6.0) \underline{d}			7.87, 7.91, 7.96.	—
3,4,6-Tri-Q-acetyl-D-glucal (VI). (44)								
3.47	5.19	4.66	4.80	5.81	5.91	5.71	7.89, 7.93, 8.01.	—
4,6-Di-Q-acetyl-3-Q-methyl-D-glucal (VII)								
3.58	5.08	6.17	4.81	(5.5 to 6.1) \underline{d}			7.90, 7.91.	6.63.
3,4-Di-Q-acetyl-D-xylal ^e (VIII).								
3.69	5.18	4.95	5.10	H _{5e} 5.79, H _{5a} 6.04.			7.91, 7.93.	—

Coupling Constants^a (c.p.s.)

	J _{1,2}	J _{2,3}	J _{3,4}	J _{4,5}	J _{5,6}	J _{5,6'}	J _{6,6'}	J _{1,3}	J _{2,4}	J _{3,5}	J _{1,5}
V	6.2	2.5 \bar{c}	4.6	1.8	() \bar{d}	1.7 \bar{c}	1.3 \bar{c}	~ 0	~ 0
VI	6.4	3.2	6.4	6.8	6.3	2.4	14.0	1.3	0.8 \bar{c}, f	0.8 \bar{c}, f	~ 0
VII	6.5	3.8	5.2 \bar{c}	6.1 \bar{c}	() \bar{d}	1.3 \bar{c}	0.8 \bar{c}	$\sim 0.8\bar{c}$	~ 0
VIII ^e	6.0 \bar{c}	4.7	3.3	J _{45e}	3.7 \bar{c} J _{45a}	2.4 \bar{c} J _{5e5a}	11.9	0.8 \bar{c}	1.5 J _{3,5e} 1.5 \bar{c} J _{1,5e}	$\sim 0, J_{1,5a}$	$\sim 0.3\bar{c}$

 \bar{d} . Not a first order system. \bar{e} . In *m*-xylene at 110°, see discussion. \bar{f} . Not reported in ref.44.

(-Cont'd)

TABLE X (Cont'd).

Chemical Shifts^a (τ).

H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H _{6'}	Acetate	Phenyl	CH ₃
3,4,6-Tri-O-acetyl-2-chloro-D-glucal (IX).									
3.28	—	4.42	4.78	(5.4 to 6.0)	\bar{d}		7.89, 7.91, 7.91	—	—
2-Acetoxy-3,4,6-tri-O-acetyl-D-glucal (X).									
3.36	—	4.43	4.78	(5.4 to 5.9)	\bar{d}		7.89, 7.89, 7.89 _s	7.93. —	—
2-Acetoxy-4,6-di-O-acetyl-3-O-mesitoyl-D-glucal (XI).									
3.32	—	4.13	4.66	(5.4 to 6.0)	\bar{d}		7.86, 7.86, 7.95	3.1 to 3.2	7.67 to 7.73
2-Acetoxy-4,6-di-O-acetyl-3-O-(2,6-dichlorobenzoyl)-D-glucal (XII)									
3.30	—	4.09	4.59	(5.3 to 6.0)	\bar{d}		7.86, 7.88, 7.96	2.7 to 2.8	—

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Coupling Constants^a (c.p.s.)

	J _{3,4}	J _{4,5}	J _{5,6}	J _{5,6'}	J _{6,6'}	J _{1,3}	J _{3,5}	J _{1,5}
IX	4.2 \bar{c}	5.6	() \bar{d}	1.1 \bar{c}	0.6 \bar{c}	~ 0
X	4.4 \bar{c}	5.6	() \bar{d}	0.9 \bar{c}	0.7 \bar{c}	~ 0
XI	4.6 \bar{c}	6.2 \bar{c}	() \bar{d}	0.7 \bar{c}	0.7 \bar{c}	$\leq 0.3\bar{c}$
XII	4.9 \bar{c}	5.8 \bar{c}	() \bar{d}	0.7 \bar{c}	0.7 \bar{c}	$\leq 0.3\bar{c}$

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TABLE X (Cont'd)

Chemical Shifts^a (τ).

H ₁	H ₂	H ₃	H ₄	H ₅	H ₆	H ₆ '	Acetate	OCH ₃
3,4,6-Tri-O-acetyl-2-nitro-D-glucal (XIII).								
1.67	—	4.01	4.73	5.26	5.52	5.80	7.89, 7.89, 7.90	—
4,6-Di-O-acetyl-3-O-methyl-2-nitro-D-glucal (XIV).								
1.80	—	5.62	4.70	5.29	5.55	5.79	7.82, 7.82	6.45
3,4,6-Tri-O-acetyl-2-nitro-D-galactal (XV).								
1.77	—	3.68	4.52	5.35	5.46	5.63	7.89, 7.89, 7.92	—
3,4-Di-O-acetyl-2-nitro-D-xylal (XVI).								
1.61	—	4.02	4.90	H _{5e} 5.46, H _{5a} 5.92			7.89, 7.89	—

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Coupling Constants^a (c.p.s.)

	J _{3,4}	J _{4,5}	J _{5,6}	J _{5,6} '	J _{6,6} '	J _{1,3}	J _{3,5}	J _{1,5}
XIII	2.9 ^c	2.0	() ^d		≤0.3	1.8 ^c	~0
XIV	2.7 ^c	1.5 ^c	8.6	4.2	12.5	≤0.3	1.9 ^c	~0
XV	5.1 ^c	4.1 ^c	3.5	4.1	12.1	≤0.3	0.4 ^c	~0
XVI	3.0	J _{45e} 2.1 ^c , J _{45a} 1.5 ^c , J _{5a5e}			12.8	≤0.3	J _{3,5e} 1.8 ^c , J _{1,5e} ~0	
							J _{3,5a} 0.6 ^c , J _{1,5a} 0.9 ^c	

Page 1 of 1

Q. No.	Q. Text	Ans.	Mark
1.	What is the value of $\sin^{-1}(\sin \frac{\pi}{6})$?	$\frac{\pi}{6}$	1
2.	What is the value of $\cos^{-1}(\cos \frac{\pi}{4})$?	$\frac{\pi}{4}$	1
3.	What is the value of $\tan^{-1}(\tan \frac{\pi}{3})$?	$\frac{\pi}{3}$	1
4.	What is the value of $\cot^{-1}(\cot \frac{\pi}{2})$?	$\frac{\pi}{2}$	1

Total Marks: 4

Q. No.	Q. Text	Ans.	Mark
5.	What is the value of $\sec^{-1}(\sec \frac{\pi}{2})$?	$\frac{\pi}{2}$	1
6.	What is the value of $\csc^{-1}(\csc \frac{\pi}{4})$?	$\frac{\pi}{4}$	1
7.	What is the value of $\operatorname{cosec}^{-1}(\operatorname{cosec} \frac{\pi}{3})$?	$\frac{\pi}{3}$	1
8.	What is the value of $\cot^{-1}(\cot \frac{\pi}{6})$?	$\frac{\pi}{6}$	1

Q. No.	Q. Text	Ans.	Mark
9.	What is the value of $\tan^{-1}(\tan \frac{\pi}{2})$?	$\frac{\pi}{2}$	1
10.	What is the value of $\cot^{-1}(\cot \frac{\pi}{4})$?	$\frac{\pi}{4}$	1

Total Marks: 10

On this basis, the relationship $J = 9.7 \cos^2 \theta$ will be assumed to apply for values of θ in the range 90° to 180° for the glycal structures in this research.

In order to obtain a relationship for θ in the range 0° to 90° , the value for $J_{4,5}$ of 1.8 c.p.s. for 3,4,6-tri-O-acetyl-D-galactal (V) was taken to give $\theta_{4,5} = 60^\circ$. This assumption seems plausible since a smaller angle would require severe Van der Waal conflict of the 4 and 5 substituents and a greater angle could only be achieved by conformational changes which, on the basis of a consideration of space-filling models (Courtaulds), introduces greater strain. Again assuming $J_{90^\circ} = 0$, the relationship $J = 7.2 \cos^2 \theta$ was obtained. These relationships are plotted in Fig. 21. It is of interest to note that these relationships are in close agreement with those originally proposed by Karplus (46) on the basis, mainly, of coupling constants obtained for acetylated sugars. The dihedral angles defined by the methine protons of the glycals studied are calculated from these relationships and given in Table XI.

Examination of Table X shows that a variety of readily determined long-range coupling interactions were obtained for the glycals listed. It was found that a relationship exists between the $J_{1,3}$ and $J_{2,3}$ values. This is not unexpected since a) the equation $J = 11 \cos^2 \theta$ has been used (47, 48) in analysis of coupling interactions in systems similar to that of H_2-H_3 , and b) allylic couplings have been shown (50, 51) to be dependent upon the angle that the C_3-H_3 bond makes with the olefinic plane (and thus upon $\theta_{2,3}$). A recent formulation (49)

Lemma 1.1. Let $f: X \rightarrow Y$ be a continuous map between topological spaces. Then f is a homeomorphism if and only if it is bijective and open (or closed).

Proof. Suppose f is a homeomorphism. Then f is bijective and open.

Conversely, suppose f is bijective and open. We show f is a homeomorphism.

Let $U \subset X$ be open. Then $f(U)$ is open by assumption. Since f is bijective, $f^{-1}(f(U)) = U$.

Let $C \subset X$ be closed. Then $f(C)$ is closed by assumption. Since f is bijective, $f^{-1}(f(C)) = C$.

Thus f is a homeomorphism. \square

Lemma 1.2. Let $f: X \rightarrow Y$ be a continuous map between topological spaces. Then f is a homeomorphism if and only if it is bijective and closed (or open).

Proof. Suppose f is a homeomorphism. Then f is bijective and closed.

Conversely, suppose f is bijective and closed. We show f is a homeomorphism.

Let $U \subset X$ be open. Then $f(U)$ is closed by assumption. Since f is bijective, $f^{-1}(f(U)) = U$.

Let $C \subset X$ be closed. Then $f(C)$ is closed by assumption. Since f is bijective, $f^{-1}(f(C)) = C$.

Thus f is a homeomorphism. \square

Lemma 1.3. Let $f: X \rightarrow Y$ be a continuous map between topological spaces. Then f is a homeomorphism if and only if it is bijective and f maps open sets to open sets.

Proof. Suppose f is a homeomorphism. Then f is bijective and maps open sets to open sets.

Conversely, suppose f is bijective and maps open sets to open sets. We show f is a homeomorphism.

Let $U \subset X$ be open. Then $f(U)$ is open by assumption. Since f is bijective, $f^{-1}(f(U)) = U$.

Let $C \subset X$ be closed. Then $f(C)$ is closed by assumption. Since f is bijective, $f^{-1}(f(C)) = C$.

Thus f is a homeomorphism. \square

Lemma 1.4. Let $f: X \rightarrow Y$ be a continuous map between topological spaces. Then f is a homeomorphism if and only if it is bijective and f maps closed sets to closed sets.

Proof. Suppose f is a homeomorphism. Then f is bijective and maps closed sets to closed sets.

Conversely, suppose f is bijective and maps closed sets to closed sets. We show f is a homeomorphism.

Let $U \subset X$ be open. Then $f(U)$ is open by assumption. Since f is bijective, $f^{-1}(f(U)) = U$.

Let $C \subset X$ be closed. Then $f(C)$ is closed by assumption. Since f is bijective, $f^{-1}(f(C)) = C$.

Thus f is a homeomorphism. \square

Lemma 1.5. Let $f: X \rightarrow Y$ be a continuous map between topological spaces. Then f is a homeomorphism if and only if it is bijective and f maps open sets to open sets.

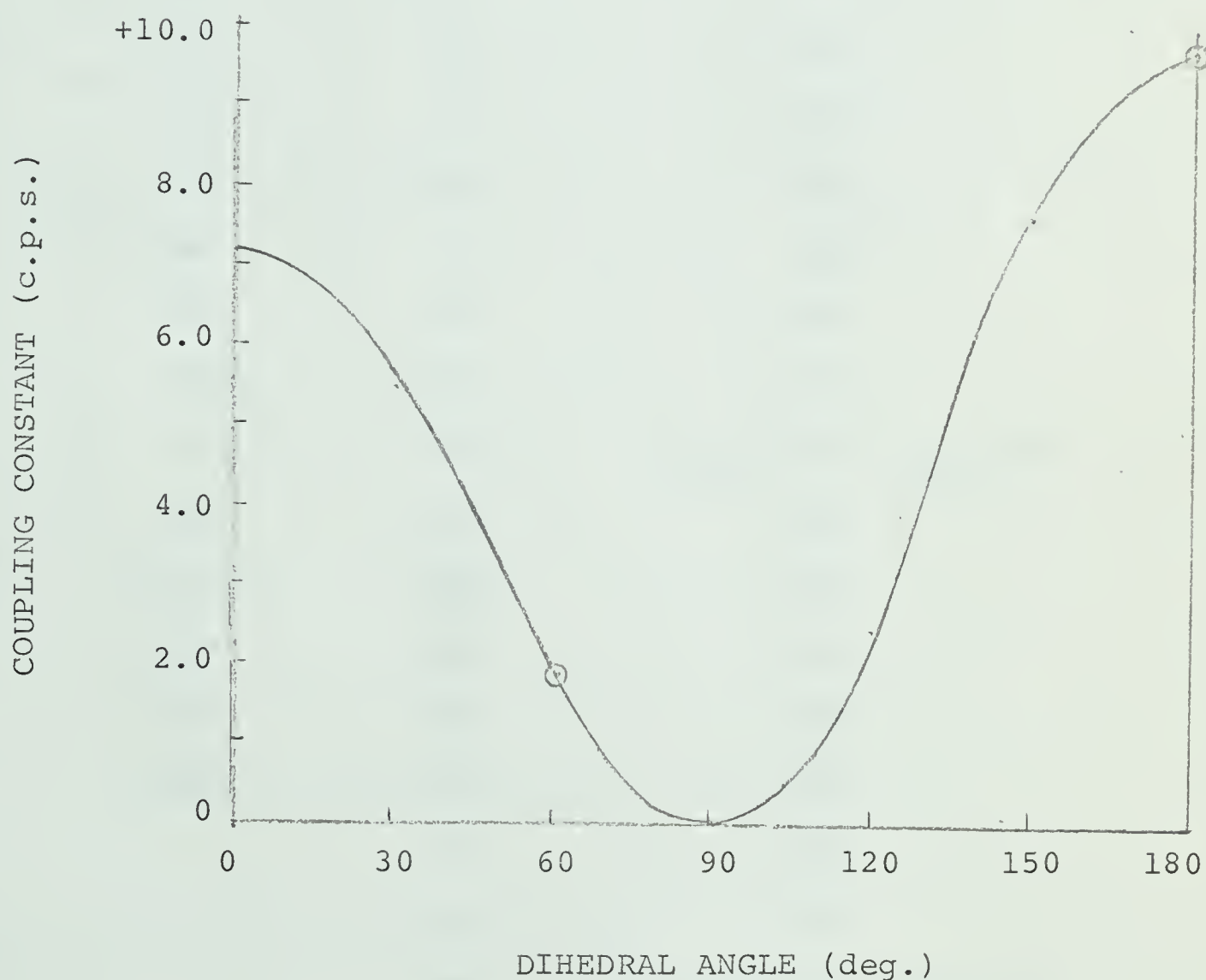


FIG. 21. The variation of coupling constant (J) with the dihedral angle (θ) between two vicinal protons.

$$J = 7.2 \cos^2 \theta \quad (0^\circ \leq \theta \leq 90^\circ)$$

$$J = 9.7 \cos^2 \theta \quad (90^\circ \leq \theta \leq 180^\circ)$$

TABLE XI

Derived Dihedral Angles

Compound	$\theta_{2,3}^{\underline{a}}$	$\theta_{3,4}^{\underline{b}}$	$\theta_{4,5}^{\underline{b}}$
I	68°	147°	180° \underline{c}
II	52°	43°	180° \underline{c}
III	52°	43°	180° \underline{c}
IV	63°	144°	159°
V	66°	37°	60° \underline{c}
VI	63°	145°	147°
VII	60°	137°	143°
VIII	57°	48°	$\theta_{4,5e}$ 44°, $\theta_{4,5a}$ 55°
IX	~60°	131°	140°
X	~57°	132°	140°
XI	~56°	134°	143°
XII	~56°	135°	141°
XIII	~40°	51°	58°
XIV	"	52°	63°
XV	"	33°	41°
XVI	"	50°	$\theta_{4,5e}$ 57°, $\theta_{4,5a}$ 63°

a. Derived from the coupling constants reported in Table X and the relationship, $J = 16 \cos^2 \theta$ ($0^\circ \leq \theta \leq 90^\circ$).

b. Derived from the coupling constants reported in Table X and the relationships, $J = 7.2 \cos^2 \theta$ ($0^\circ \leq \theta \leq 90^\circ$) and $J = 9.7 \cos^2 \theta$ ($90^\circ \leq \theta \leq 180^\circ$).

c. The dihedral angles assumed to derive the above expressions.

$$J = 6.6 \cos^2 \theta + 2.6 \sin^2 \theta \quad (0^\circ \leq \theta \leq 90^\circ)$$

for systems such as H_2-H_3 has been shown to be incorrect by Anet (112) and also by the present work, since it predicts a minimum $J_{2,3}$ value of 2.6 c.p.s.

Rather than use the expression $J = 11 \cos^2 \theta$ proposed by Smith and Kriloff (47) for estimating the dihedral angles defined by the 2 and 3 protons of allylic systems, the expression $J = 16 \cos^2 \theta$ was derived from the present data. This was accomplished by assuming that the sum of the dihedral angles defined by the 2 and 3 protons of compounds I and II is 120° . It follows then that

$$J_{2,3} = x \cos^2 \theta = 2.2,$$

and $J'_{2,3} = x \cos^2 (120 - \theta) = 5.9,$

for compounds I and II, respectively.

Therefore
$$\frac{\cos (120 - \theta)}{\cos \theta} = \left(\frac{5.9}{2.2} \right)^{0.5} = 1.62.$$

Since
$$\cos (a - b) = \cos a \cdot \cos b + \sin a \cdot \sin b,$$

$$\frac{\cos 120^\circ \cdot \cos \theta + \sin 120^\circ \cdot \sin \theta}{\cos \theta} = 1.62$$

and
$$0.50 \cos \theta + 0.86 \sin \theta = 1.62 \cos \theta,$$

By substitution and collection of terms,

$$0.86 (1 - \cos^2 \theta)^{0.5} = 1.12 \cos \theta$$

and
$$0.75 - 0.75 \cos^2 \theta = 1.26 \cos^2 \theta.$$

Therefore
$$0.75 = 2.01 \cos^2 \theta$$

and
$$\cos \theta = 0.611.$$

It then followed that the dihedral angles defined by the 2 and 3 protons of I and II are 68° and 52° , respectively. These angles are consistent with those values found by Corey and Sneed (53) and by Abraham et al. (48). The equation $J_{2,3} = 16 \cos^2 \theta_{2,3}$ provides $\theta_{2,3}$ values for all glycals bearing a proton at C-2.

It was found that a plot of the values for $\theta_{2,3}$ against the coupling between the 1 and 3 protons gave the curve shown in Fig. 22. The smoothness of the curve is such that it should be possible to estimate the dihedral angle defined by a substituent at the 2-position of glycals and the 3-proton from the value of $J_{1,3}$.

Before use could be made of the dihedral angles in Table XI, it was necessary to examine the errors inherent in their determination. The possible sources are as follows;

- (a) Time-averaging of different conformations,
 - (b) Experimental errors in determining spacings in P.M.R. spectra,
 - (c) The use of first-order analyses in determining the coupling constants,
 - (d) Assumptions made regarding the validity of the derived Karplus relationship,
 - (e) Electronegativity and angular dependence effects on spin-spin coupling,
- and (f) Solvent effects on conformation.

In most cases, the dihedral angles have been expressed to the nearest degree for the purpose of consistency within the set of conformational analyses. These values are probably within a few degrees of the actual values, and it should be made clear

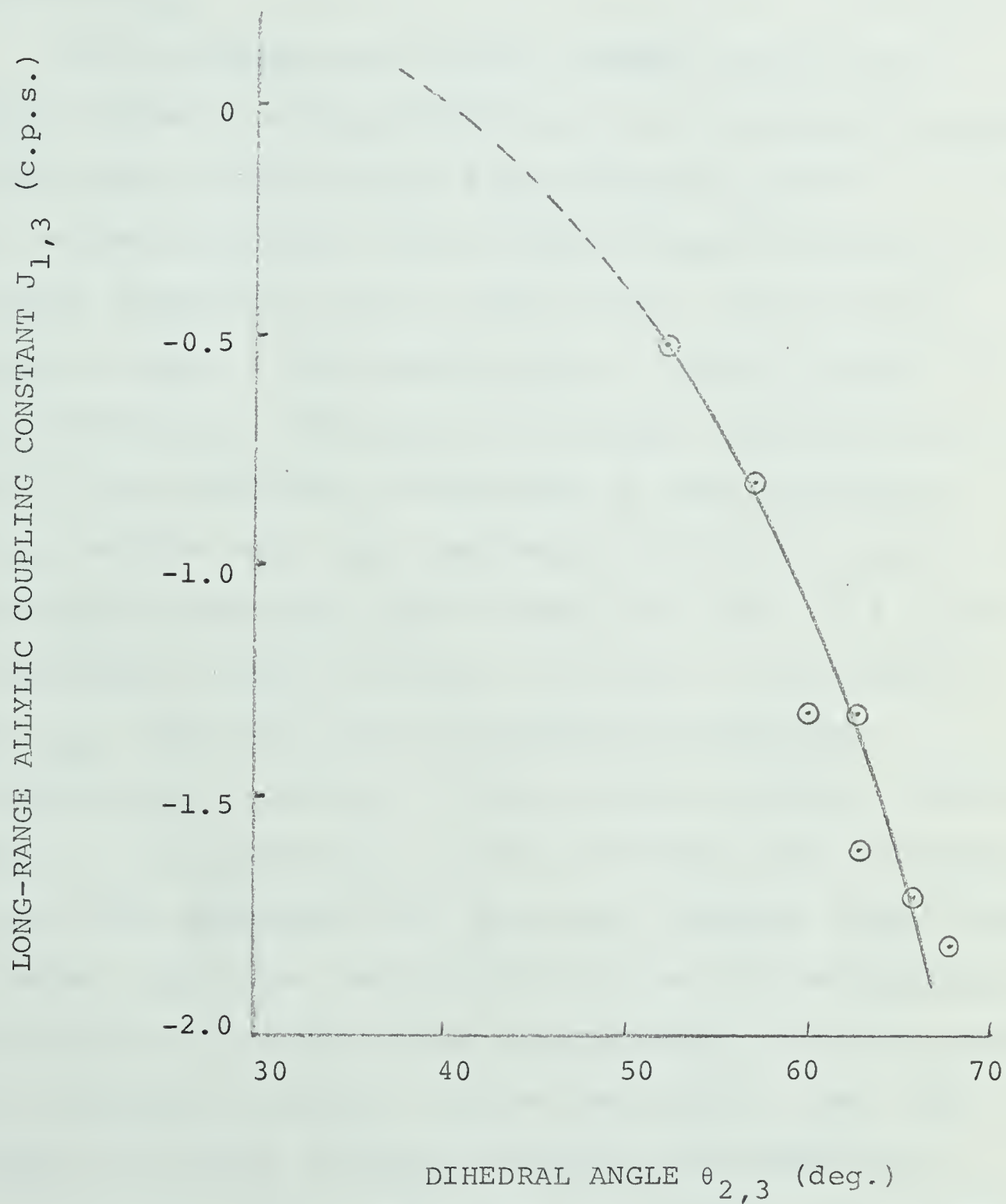


FIG. 22. The variation of the observed long-range allylic coupling, $J_{1,3}$, with the calculated dihedral angle, $\theta_{2,3}$.

that having expressed their value to the nearest degree does not indicate that these values have been used to such a degree of accuracy. The value in so expressing these angles lies in the consistency within a series of compounds, rather than in their absolute values.

Time-averaging will either produce two sets of coupling constants or one averaged set or an indistinct mixture dependent upon the rate of the time-averaging process. As shown in the following section, time-averaging does not occur at $35 \pm 2^\circ$, the ambient temperature of the spectrometer. The coupling constants in Table X were demonstrated, wherever doubtful, by double irradiation. Each coupling constant recorded was an average of all splittings attributable to that particular coupling, and the error was considered to be ± 0.1 c.p.s. Those couplings expressed approximately as, e.g., ~ 9.5 c.p.s., were considered to have an error ± 0.2 c.p.s. The values of J_{0° and J_{180° that were used to establish the Karplus relationships were probably the main source of error. However, no better set of appropriate P.M.R. parameters were available and, since only approximate but consistent dihedral angle values were needed, and since a self-consistent set of conformational analyses were derived from these relationships, they are judged to be sufficiently accurate for the uses made of them. The dependence of vicinal coupling constants upon substituent electronegativity (67) is well known and recently it has been suggested (113) that electronegativity effects are angularly dependent. Therefore, even in a system with constant electronegativity effects, the observed coupling constants can

deviate from a $\cos^2\theta$ relationship. Allylic long-range couplings have also been shown to be sensitive to substituent electronegativity changes (114, 115) and to double bond delocalization (50). However, all the dihedral angles derived in Table XI were from the fast-changing portions of the curves in Figures 21 and 22, i.e. where large changes in coupling constants produce small changes in dihedral angles. Thus electronegativity effects should be minimal.

As a recent review (116) has shown, many examples are known of time-averaging at 35°. In the present conformational analysis it was necessary to eliminate this possibility. Several glycols were examined and evidence for time-averaging was found only in one case, tri-O-acetyl-2-nitro-D-galactal (XV), an example where time-averaging had been considered possible. Each glycol had its spectrum recorded at 35° in the stated solvent before changing the temperature. The effect of temperature on the spectra of a series of configurationally homogeneous compounds (VI, XI and XIII) was examined to observe the effect of increasing $A^{(1,2)}$ strain (60). Increase of the $A^{(1,2)}$ strain may elevate the energy of the ground state enough to allow slow interconversion with another conformation. No evidence of such interconversions was found. However, all three showed slow rotation about C_5-C_6 at 110°. Compound VIII was observed at 110° in *m*-xylene primarily to obtain a first order spectrum of this compound. No evidence of interconversion was noted.

The spectrum of compound XV at 35° contained a singlet (H_1), a doublet with a spacing of 5 c.p.s. (H_3) and a quartet with spacings of 4 and 5 c.p.s. (H_4) in both $CDCl_3$ and toluene. When a toluene solution of XV was cooled to -55°, the P.M.R. spectrum again showed H_1 as a singlet, but H_3 was now a poorly defined doublet with a spacing of 5 c.p.s., and H_4 one broad signal with a $W_{\frac{1}{2}} > 10$ c.p.s. By comparison, the methyl signal of the toluene solvent had a $W_{\frac{1}{2}} = 2$ c.p.s. Examination of molecular models (Courtaulds) shows that the gauche interactions between C-3 acetoxy, C-4 acetoxy and C-5 acetoxymethylene are similar in all staggered conformations, but that relief of the $A^{(1,2)}$ interaction is offset by an increase in the across-ring interaction between the C-3 and C-5 groups as they become more axially oriented. Therefore the energies of the more stable conformations may be similar.

For all compounds except XV, there were two possible situations. First, one conformation can be so highly favored that even if interconversion slowed or ceased on cooling, no significant change would be seen. Second, interconversion may be so rapid at 35° that cooling to -30° would not slow the interconversion sufficiently to produce observable changes. The slow rotation about C_5-C_6 at 110° for VI, XI and XIII demonstrates that even this interconversion has a high energy of activation, and it should be remembered that ring conformational changes encounter several similar barriers simultaneously. The self-consistent trends in couplings and

chemical shifts (see Table X) strongly suggest a series of fixed conformations. Thus, the second situation is highly improbable, and it can be concluded that except in the P.M.R. spectrum of XV, time-averaging played no significant role in this study.

In the foregoing discussion, the theoretical and experimental bases for the interpretation of the P.M.R. spectra of the substituted glycals listed in Table X were developed. A conformational analysis of these glycals will now be presented.

In order to gain an appreciation of the strainless conformations for glycals, a molecular model of 3,4-dihdropyran was made and the effect of changing the dihedral angle ($\theta_{2,3}$) defined by the 2 and 3 protons on the remainder of the molecule was examined. It was found that for each angle, two relatively strainless conformations were possible. A number of these conformations are depicted in Fig. 23. Conformation A represents the half-chair conformation often referred to as H1 (117). In this conformation $\theta_{2,3}$ is about 70° . The alternate relatively strainless conformation which maintains this angle is in between conformations B and BC and consequently inherently less favorable (52, 54). These latter conformations are normally referred to as the boat and half-boat conformations, respectively. If $\theta_{2,3}$ is 50° then the compound has either the half-chair (1H) of C or a conformation in between D and AD. In the boat conformations B

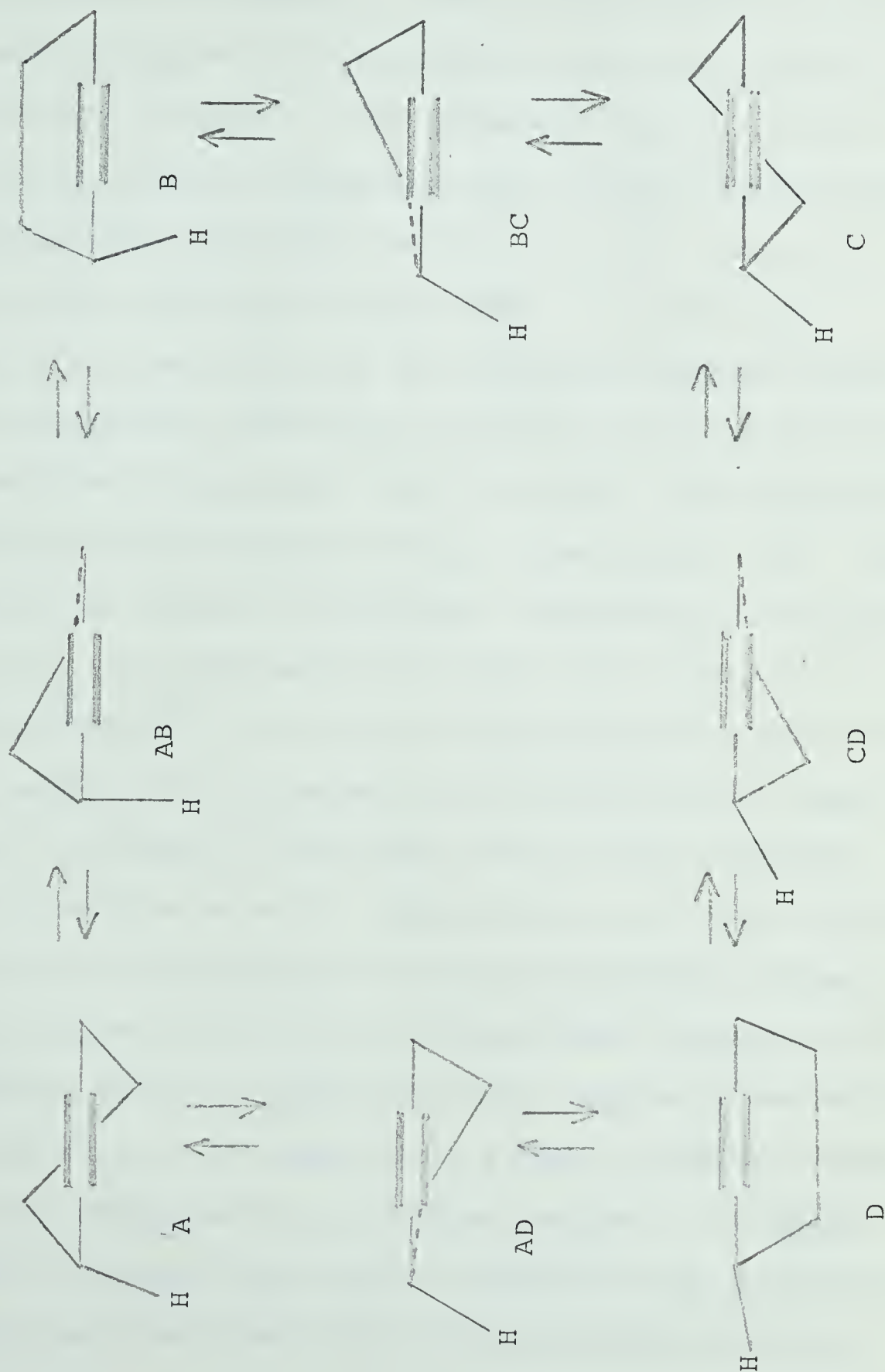


Fig. 23. The relatively strainless conformations encountered as $\theta_{2,3}$ is varied between 10° and 110° for 3,4-dihydropyran.

and D, $\theta_{2,3}$ is $\sim 110^\circ$ and $\sim 10^\circ$, respectively. In the half-boat conformations AB, BC, CD and AD, the values for $\theta_{2,3}$ are $\sim 90^\circ$, 60° , 30° and 60° respectively. It would be desirable to assign conformations on the basis of these considerations which themselves are based on the assumption that all valence angles are $109^\circ 28'$. However, it was observed that the P.M.R. parameters of certain compounds could not be rationalized in this way without straining the ring in such a way as to cause general flattening of the model. In fact, this flattening was required only for compounds wherein severe gauche interactions could not be relieved through conformational change and Hendrickson (66) has calculated that appreciable flattening can be achieved without undue strain (65). This process can so change a half-chair conformation that the value of $\theta_{2,3}$ can approach 60° rather than assume the expected 50° or 70° . In view of these complications it has proven ineffectual to discuss the conformations of these compounds in terms of half-boats, half-chairs and boats. Boat-like conformations were not encountered and, since half-chair and half-boat conformations are stereochemically closely related, the results of this conformational analysis will be discussed in terms of quasi-half-chair conformations while presenting what is believed to be a fairly precise geometry through the presentation of dihedral angles. The quasi-half-chair conformations will be referred to as q-H1 and q-1H following the usual practice for designating half-chair conformations.

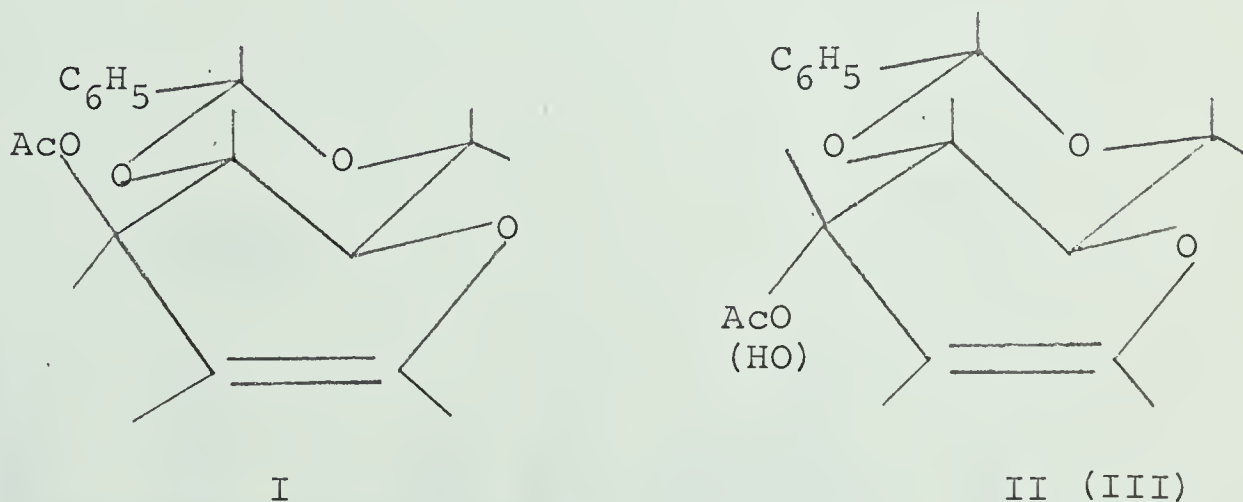
Chemical shifts (τ) for compound I were: H_1 , 3.65; H_2 , 5.24; H_3 , 4.48; H_4 , H_5 and both H_6 , 5.5 to 6.3; phenyl, 2.5 to 2.8; benzylidene, 4.45; acetate, 7.95; and the coupling constants (c.p.s.) were: $J_{1,2}$, 6.2*; $J_{2,3}$, 2.2*; $J_{3,4}$, 6.8 (uncertain), $J_{1,3}$, 1.8*, $J_{2,4}$ and $J_{1,5} \sim 0^*$, $J_{3,5} \leq 0.3$. The asterisks indicate that the assignment of those coupling constants were confirmed by spin-spin decoupling when deuteriochloroform was the solvent.

"Tickling" experiments (118) were performed to determine the sign of $J_{1,3}$. Observation of H_2 during weak irradiation of the high-field signal (τ 4.528) of H_3 led to partial collapse of the high-field portion of the H_2 quartet. Therefore, coupling constants $J_{1,2}$ and $J_{2,3}$ have the same relative sign. General experience (119) has been that both these types of vicinal couplings always have positive values. Weak irradiation of the lowest-field signal (τ 3.586) of H_1 led to partial collapse of the high-field portion of the H_2 quartet, thus showing that $J_{1,3}$ has an opposite sign to $J_{2,3}$, i.e. $J_{1,3} = -1.8$ c.p.s.

In order to obtain a spectrum with greater chemical shifts between the protons, a solution of I in benzene was examined. Unfortunately, the C_{13} satellite of the solvent coincided with the C_3 proton. However, use of benzene- d_6 as solvent removed this difficulty. The P.M.R. parameters obtained under these conditions are reported in Table X and the spectrum recorded in Fig. 24.

The couplings in Table X do not include mention of coupling with the benzyldiene proton. The signal for this proton is broader than expected for an uncoupled proton and irradiation of H_4 or H_5 produced an ill-defined doublet. However, the irradiating signal was probably strong enough to affect weak couplings involving the adjacent H_6 signals. Irradiation of the benzyldiene proton appeared to reduce the width of the signals of H_{6e} and H_4 , but not those of H_5 or H_{6a} . It was concluded that $J_{4,Benz}$ and/or $J_{6e,Benz} \leq 0.5$ c.p.s.

The conformation of I was assumed to be the H1 half-chair conformation by reason of the dioxan ring being fused to the flexible portion of the glycal ring and the lack of any large distorting influence in this conformation.



Compounds II and III, like I, were assumed to have the H1 conformation for the same reasons. The P.M.R. spectrum of II (Fig. 25 and Table X) was readily interpreted on a first order basis, but that of III required extensive decoupling for

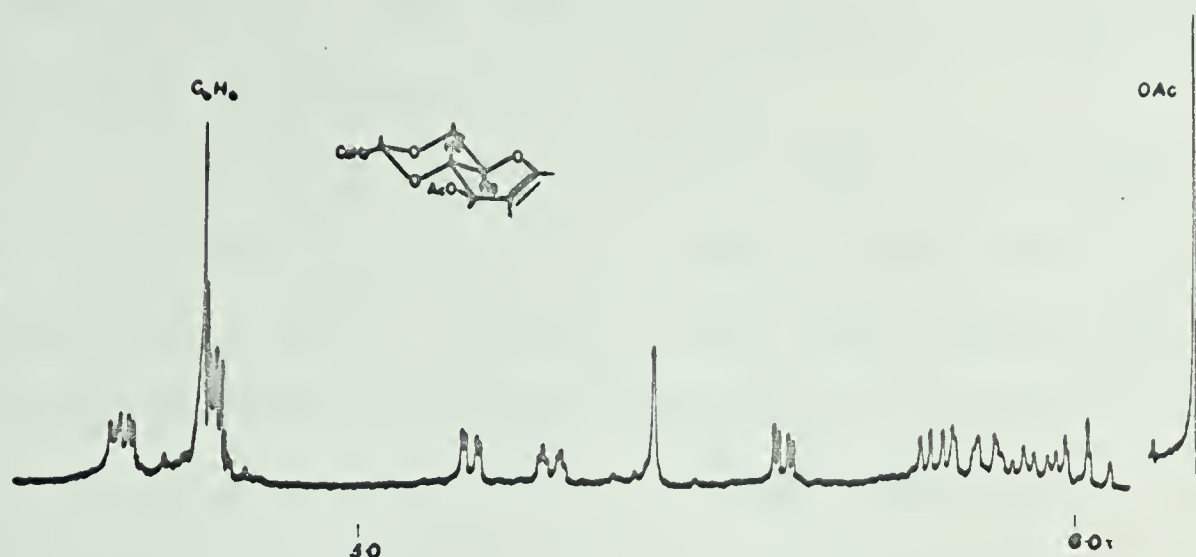


FIG. 24. P.M.R. spectrum in benzene-d₆ (100 Mc.p.s.) of 3-O-acetyl-4,6-O-benzylidene-D-glucal⁶ (I). (Acetoxy offset) DISCUSSION, Section 1.

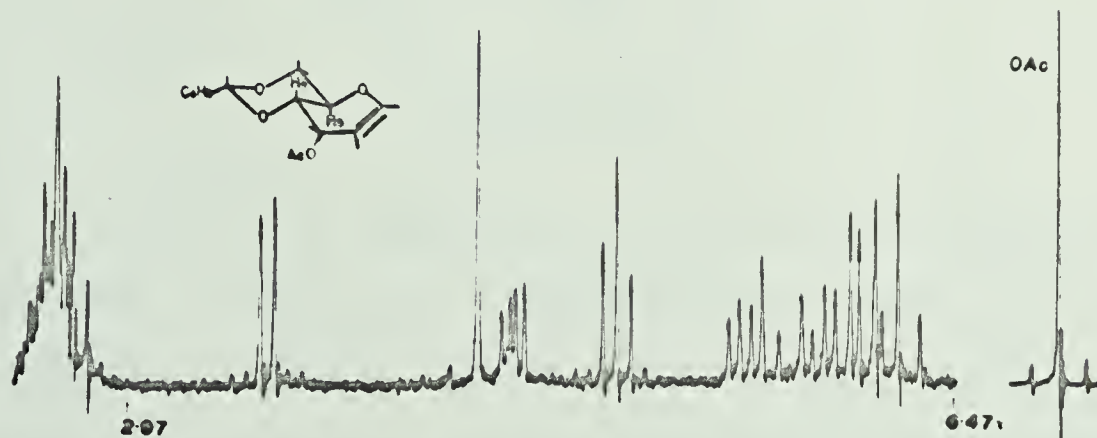
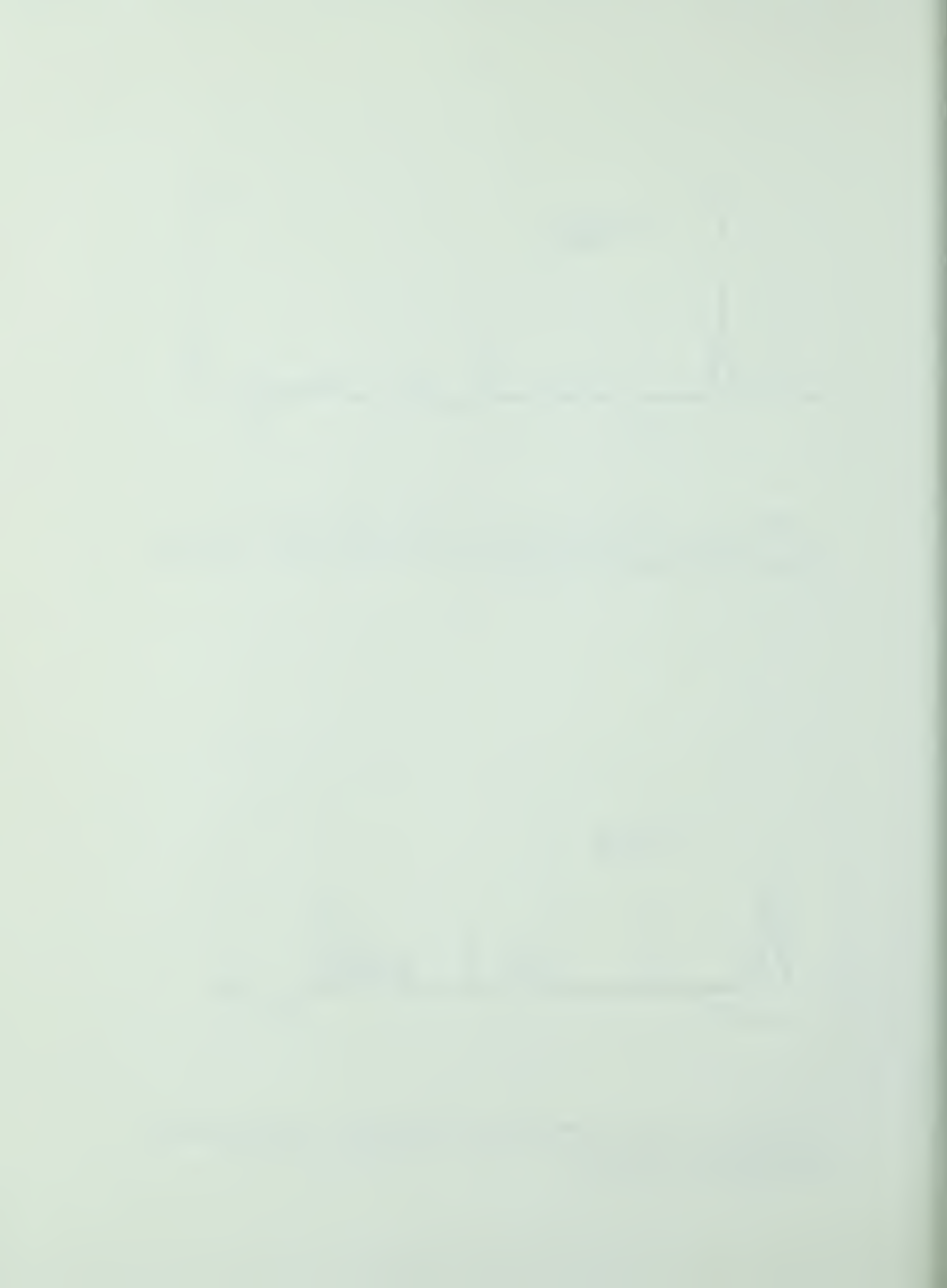
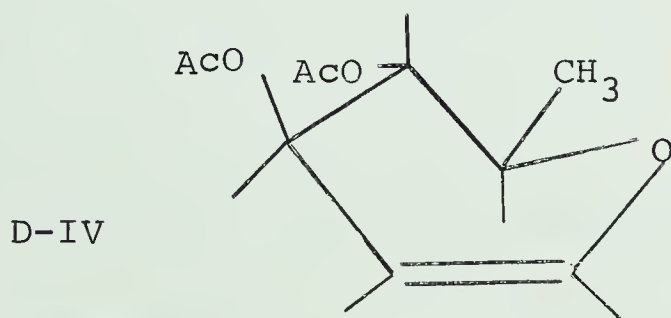


FIG. 25. P.M.R. spectrum (100 Mc.p.s.) of 3-O-acetyl-4,6-O-benzylidene-D-allal (II). (Acetoxy offset.) DISCUSSION, Section 1.

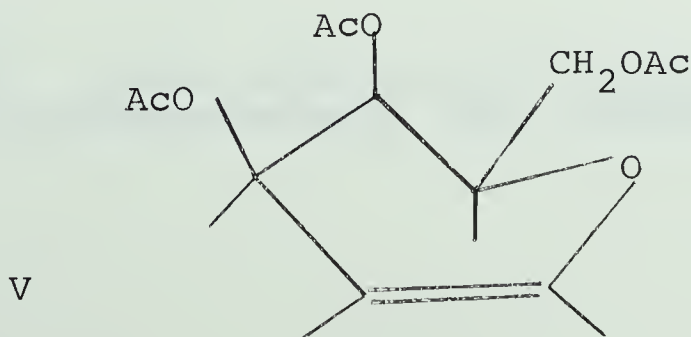


a full interpretation since H_3 and H_5 had almost identical chemical shifts. The benzyldiene proton of II was coupled to H_{6e} by approximately 0.5 c.p.s.

For di-O-acetyl-L-rhamnal (IV), the minimum values for $\theta_{3,4}$ and $\theta_{4,5}$ are 60° and these values would apply to the D-enantiomer (D-IV). Thus only the larger angles were taken into consideration and the value for $J_{4,5}$ (Table X) indicated that $\theta_{4,5}$ is less than 180° , probably about 160° . Indeed when the values for $\theta_{2,3}$ and $\theta_{3,4}$ were imposed on a model, the value for $\theta_{4,5}$ was about 160° . In this conformation it was evident that the ring was flatter than in the regular H1 conformation and it is best described as a q-H1 conformation. The P.M.R. spectrum (Fig. 2) has three long-range couplings which will be dealt with later.



The P.M.R. spectrum of tri-O-acetyl-D-galactal (V) is reported in Fig. 26. The requirement that $\theta_{4,5} \approx 60^\circ$ was discussed earlier. The values for $\theta_{2,3}$ and $\theta_{3,4}$ are in good general agreement for an only slightly distorted H1 conformation.



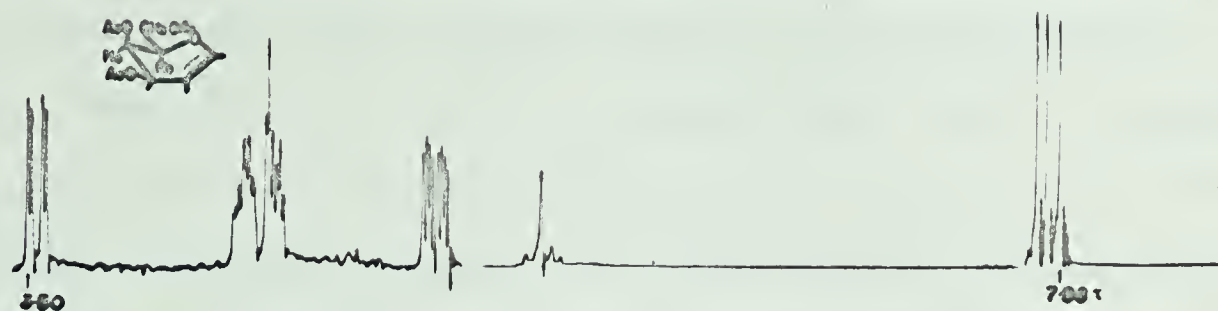


FIG. 26. P.M.R. spectrum (100 Mc.p.s.) of 3,4,6-tri-O-acetyl-D-galactal (V). (H_5 , two H_6 and the acetates are at reduced amplitude). DISCUSSION, Section 1.

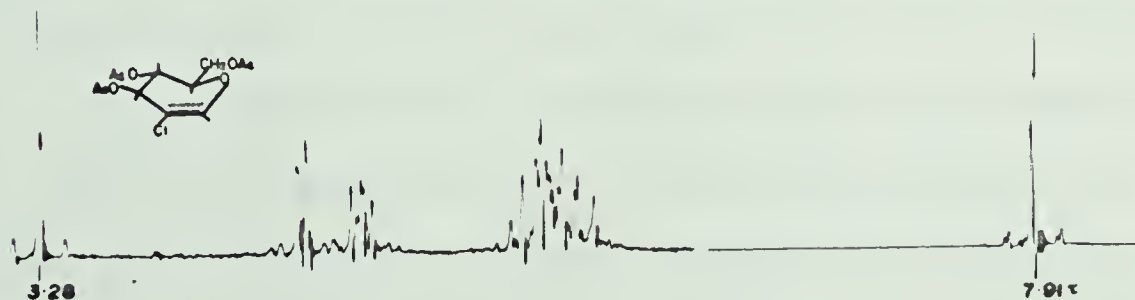
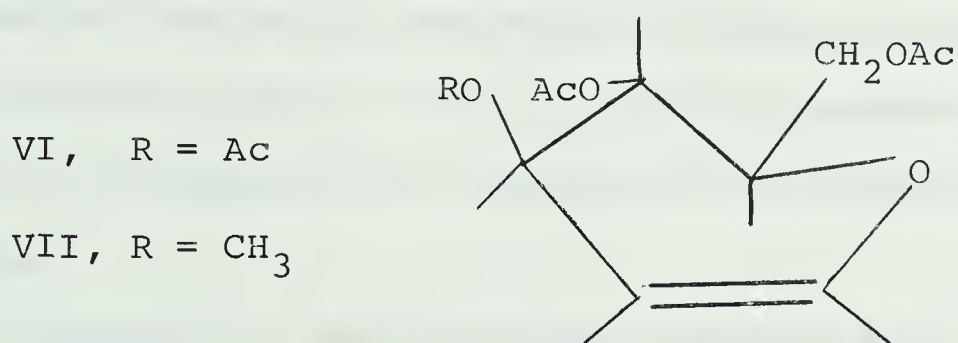


FIG. 27. P.M.R. spectrum (100 Mc.p.s.) of 3,4,6-tri-O-acetyl-2-chloro-D-glucal (IX). DISCUSSION, Section 1.

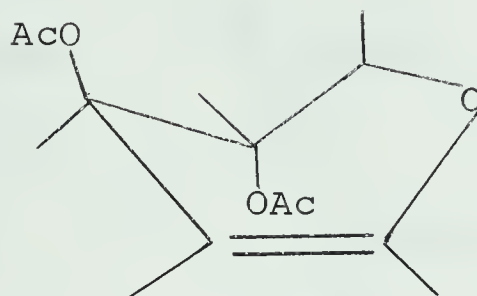
As seen in Table X, the introduction of an acetoxy at the 6-position of D-IV to give tri-O-acetyl-D-glucal (VI) resulted in an apparent small decrease in $\theta_{4,5}$. This would be in accord with the greater bulk of the acetoxymethyl group. When the $\theta_{2,3}$ and $\theta_{3,4}$ values were set on a model, flattening of the ring was required and $\theta_{4,5}$ became $\sim 155^\circ$. The same situation existed for 4,6-di-O-acetyl-3-O-methyl-D-glucal (VII).



The P.M.R. parameters for VI were the same as those found by Hall and Johnson (44) at 100 Mc.p.s. in benzene. The P.M.R. spectrum of VII at 100 Mc.p.s. in deuteriochloroform was previously shown in Fig. 3.

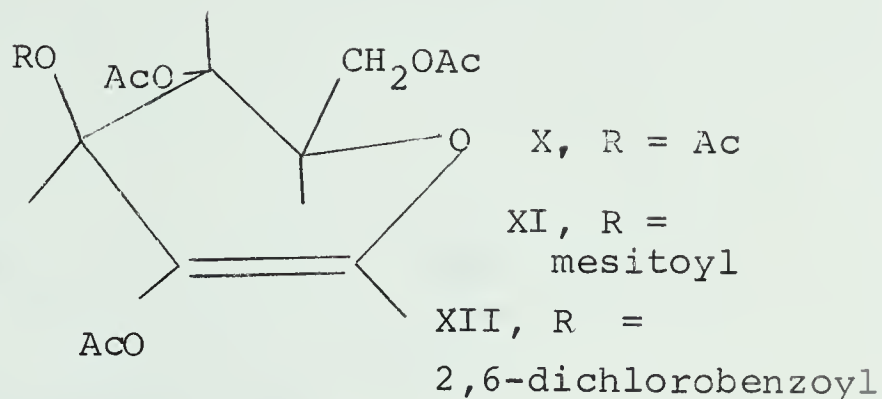
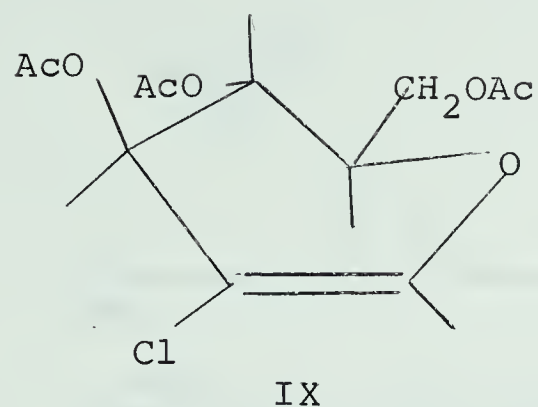
The P.M.R. spectrum of di-O-acetyl-D-xylal (VIII) in deuteriochloroform at 35° was almost entirely non-first order. In *m*-xylene at 35° , a considerable improvement was found and, when heated to 100° , sufficient separation of H₂, H₃ and H₄ was produced to allow a first-order analysis. This spectrum was previously presented in Fig. 4. The q-lH conformation was clearly indicated by the values for $\theta_{4,5e}$ and $\theta_{4,5a}$. When the derived $\theta_{2,3}$ and $\theta_{3,4}$ angles were set on the model it was found that $\theta_{4,5}$ values were indeed approximately 60° . The conformation of VIII requires that the acetoxymethyl

VIII



group of VI is mainly responsible for that compound adopting the q-H1 conformation. In the q-1H conformation, VI would have opposition of the axial acetoxymethyl group with the quasi-axial 3-acetoxy group. This interaction appears sufficiently great in a q-1H conformation to render the q-H1 conformation more favorable.

The compounds IX and X are the 2-chloro and 2-acetoxy derivatives of VI, respectively, and represent glucals with a medium $A^{(1,2)}$ interaction (60). The P.M.R. parameters are reported in Table X and the spectra presented in Figs. 27 and 28. The only way in which all three dihedral angles could be accommodated was to have C_4 above C_5 and the ring in a flattened q-H1 conformation, perhaps closer to the half-boat than the half-chair. As will be seen later, some D-glucals do have the q-1H conformation in which case the P.M.R. parameters were quite different from those found for these two compounds. The substitution of the 3-acetoxy group in X by the mesitoyloxy and 2,6-dichlorobenzoyloxy groups to give compounds XI and XII produced little change in the P.M.R. parameters (Table X and Figs. 29 and 30) and therefore probably did not create substantially greater $A^{(1,2)}$ interactions.



In view of the great similarity of their P.M.R. parameters, the compounds XIII, XIV and XVI (Figs. 8, 9 and 11, respectively) were considered together. For XIII, the values of the dihedral angles $\theta_{3,4}$ and $\theta_{4,5}$ were taken to be 51° and 58° , respectively, from the following reasoning. From Fig. 21, the alternative dihedral angle values are 123° and 117° , respectively, and they could be accommodated as follows. The boat D must be expected to be

	<u>Boat</u>	<u>Half-boat</u>	<u>Half-boat</u>	<u>Half-chair</u>
	D	AD	CD	C
$\theta_{3,4}$	51°	123°	51°	123°
$\theta_{4,5}$	117°	117°	58°	58°

an unfavorable conformation because of the eclipsing experienced in the flexible portion of the ring. The $\theta_{2,3}$ values of $\sim 60^\circ$ and $\sim 50^\circ$ expected for half-boat AD and half-chair C are too large for the observed $\theta_{2,3}$ ($\sim 40^\circ$, Fig. 22). Furthermore, the large observed $J_{3,5}$ value is usually associated with a planar "W" shape and this stereochemical configuration is best given by half-boat CD, i.e. a q-1H conformation. This latter conformation allows

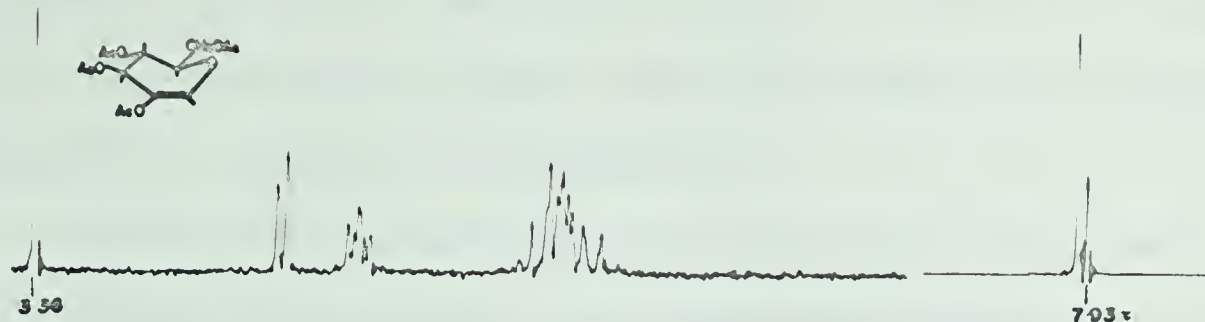


FIG. 28. P.M.R. spectrum (100 Mc.p.s.) of 2-acetoxy-3,4,6-tri-O-acetyl-D-glucal (X). (DISCUSSION, Section 1.)

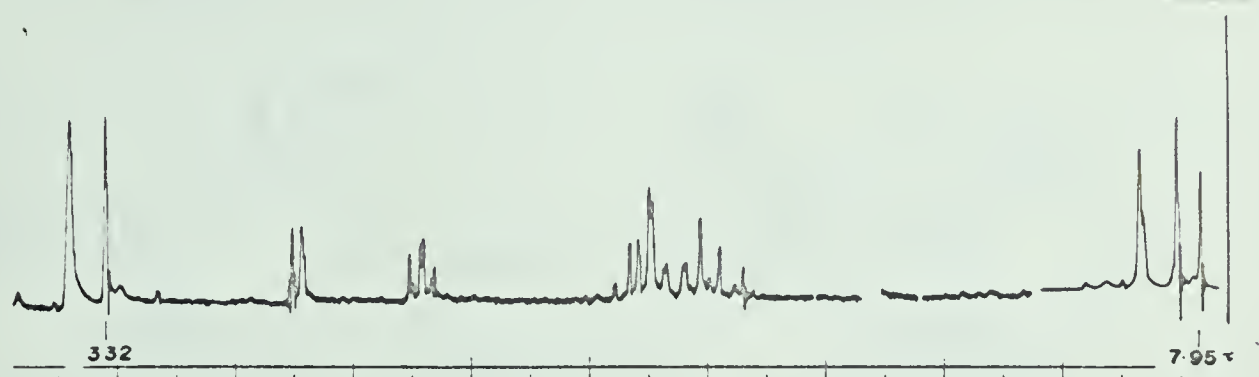


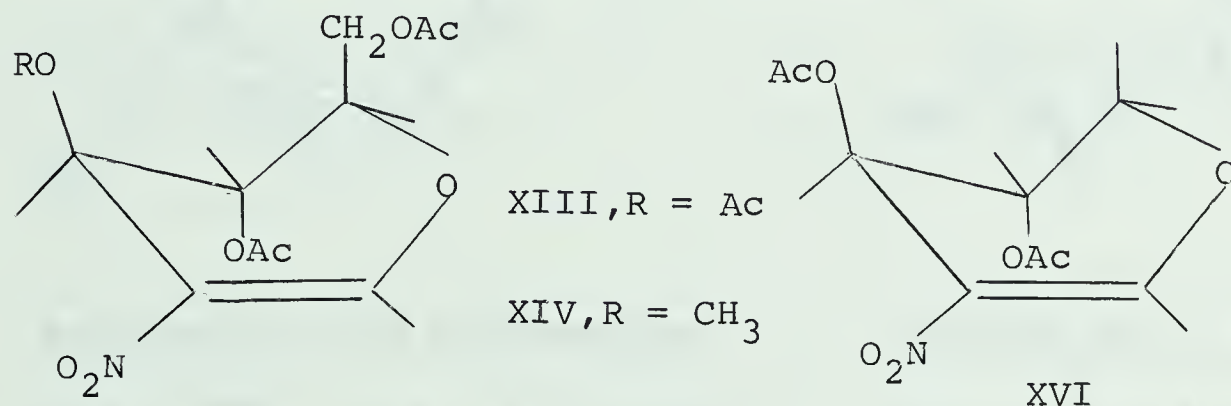
FIG. 29. P.M.R. spectrum (100 Mc.p.s.) of 2-acetoxy-4,6-di-O-acetyl-3-O-mesitoyl-D-glucal (XI). (DISCUSSION, Section 1.)



FIG. 30. P.M.R. spectrum (100 Mc.p.s.) of 2-acetoxy-4,6-di-O-acetyl-3-O-(2,6-dichlorobenzoyl)-D-glucal (XII). (DISCUSSION, Section 1.)

the greatest relief of the $A^{(1,2)}$ strain of any of the four possible conformations, except the boat D which was already eliminated for reasons of eclipsing.

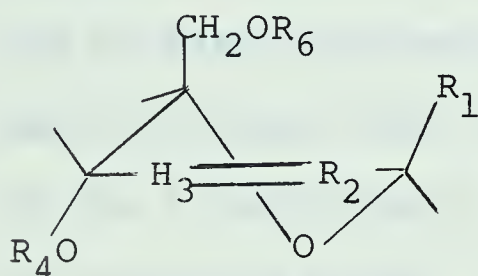
The P.M.R. parameters of XVI can only be accommodated by such a q-1H conformation. The observed value of $J_{1,3}$ is much smaller than that of compound XVI, which suggests that the 3-acetoxy function in XVI is much more axially disposed than that in VIII.



The P.M.R. parameters (44) for 3,4,6-tri-O-acetyl-D-glucal (VI) have already been taken into account. 3,4,6-Tri-O-acetyl-D-gulal has also been described (120), but from the few P.M.R. parameters provided, appears to possess a non-first order spectrum. These are the only 1,2-unsaturated sugars for which a set of P.M.R. parameters have been published.

However, a considerable body of P.M.R. data is available for 2,3-unsaturated systems, including six α/β pairs of compounds. Ferrier, Overend and Sankey (121) provided P.M.R. parameters for three pairs of pseudo-D-glucals, Anet (112) studied a pair of pseudo-D-glucals and a pair of pseudo-D-galactals, and Lemieux and Bose (99) prepared a pair of pseudo-

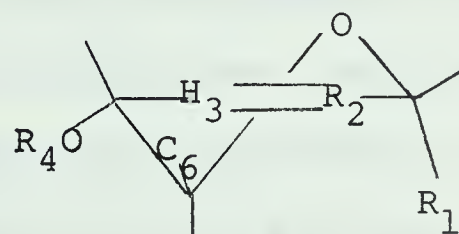
D-glucals. In all pseudo-D-glucal examples, the α -anomer has coupling constants $J_{3,4} \sim 2$ c.p.s. and $J_{4,5} \sim 9$ c.p.s. The β -anomer has $J_{3,4} \sim 5.5$ c.p.s. and $J_{4,5} \sim 2$ c.p.s. Along with the pseudo-D-galactals and other examples (99, 121, 122), these parameters clearly demonstrate that these 2,3-unsaturated systems exist in either the 1H or H1 half-chair conformations, the choice being dictated by the anomeric configuration.



β -anomer has 1-H conformation

$$\theta_{3,4} \sim 50^\circ \rightarrow J_{3,4} \sim 5.5 \text{ c.p.s.}$$

$$\theta_{4,5} \sim 60^\circ \rightarrow J_{4,5} \sim 2 \text{ c.p.s.}$$



α -anomer has H-1 conformation

$$\theta_{3,4} \sim 70^\circ \rightarrow J_{3,4} \sim 2 \text{ c.p.s.}$$

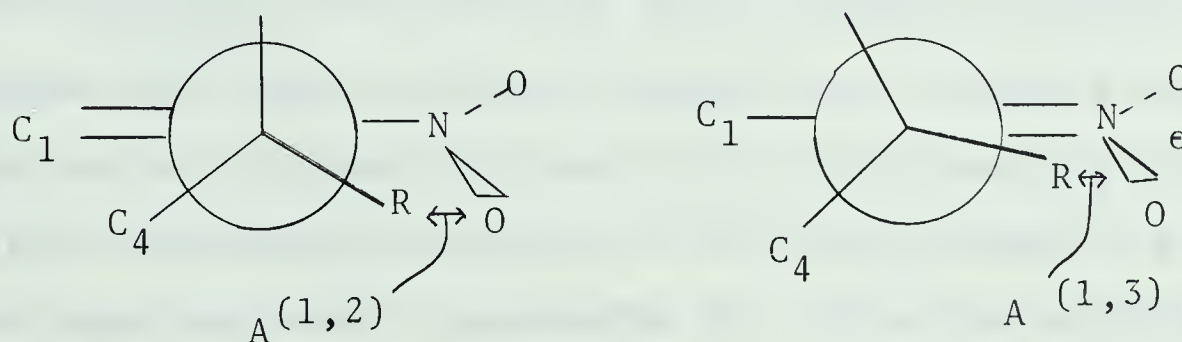
$$\theta_{4,5} \sim 170^\circ \rightarrow J_{4,5} \sim 9 \text{ c.p.s.}$$

The pseudo-axial anomeric substituent is the better positioned in view of both the $A^{(1,2)}$ strain hypothesis (60) and the anomeric effect (84, 123). Since both these effects must be opposed in achieving the alternative half-chair form, it can be readily seen why the anomeric configuration determines the conformation.

The $J_{3,4}$ and $J_{4,5}$ parameters in these systems not only are readily accommodated by the J versus θ relationships developed in the present study, but strongly support them. It is perhaps significant that no $J_{1,3}$ parameters are reported for these 2,3-unsaturated systems, because the present work

predicts only weak coupling by H-3 to the invariably pseudoequatorial H-1.

The changes of conformation in the series of acetylated 2-substituted-D-glucals reflect the magnitude of the $A^{(1,2)}$ interaction (60) between the substituents at the 2- and 3- positions. Comparison of the changes in conformations in the series of 3,4,6-tri-O-acetyl-2-R-D-glucals where R = H, Cl, OAc and NO₂, respectively, (VI, IX, X and XIII) and of the 2-acetoxy-4,6-di-O-acetyl-3-O-R'-D-glucals (X, XI and XII) shows that the main factor is the steric requirement of the 2-substituent (R) in pseudoequatorial orientation as indicated below. The 2-nitro group has the greatest $A^{(1,2)}$ effect and this is readily attributed to the need for coplanarity of the whole nitroolefin system for conjugation. That strong configuration is present can be seen by inspection of the nitro asymmetric stretching frequencies presented in Tables XV and XX.



It is convenient here to distinguish between the $A^{(1,2)}$ and $A^{(1,3)}$ effects. These arise in systems containing endo- and exo- cyclic double bonds and can both have large magnitudes where the group R in the above structures is either pseudoequatorial or equatorial. The $A^{(1,3)}$

effect was used in the Introduction in a rationalisation of the products of nitromethane condensations, and is used extensively to explain the reaction routes of the acetylated 2-nitroglycals XIII and XVI with methanol (DISCUSSION, Sections 4 and 5).

Allylic long-range coupling has been previously shown (50, 51) to be dependent upon the angle that the allylic C-H bond defines with the olefinic plane. Figure 22 shows that a relationship exists, and the formula

$$J = 1.3 \cos^2 \theta - 2.6 \sin^2 \theta, (0^\circ \leq \theta \leq 90^\circ)$$

has been proposed by Garbisch (49). Models of compounds mentioned in Sternhell's review (50) indicate that when $\theta \simeq 0^\circ$, $J_{1,3}$ is usually one to two c.p.s. The examples considered by Barfield (51) also demonstrate this characteristic. Therefore, $J_{1,3}$ coupling does not only involve contact with the π -orbitals, but also some other coupling mechanism. Since maximum long-range coupling through four saturated bonds is experienced in planar systems (50), it is possible that a similar mechanism can operate in allylic systems to give non-zero couplings when θ approaches 0° . Thus the complete relationship must be of the type, and magnitude, suggested by Garbisch.

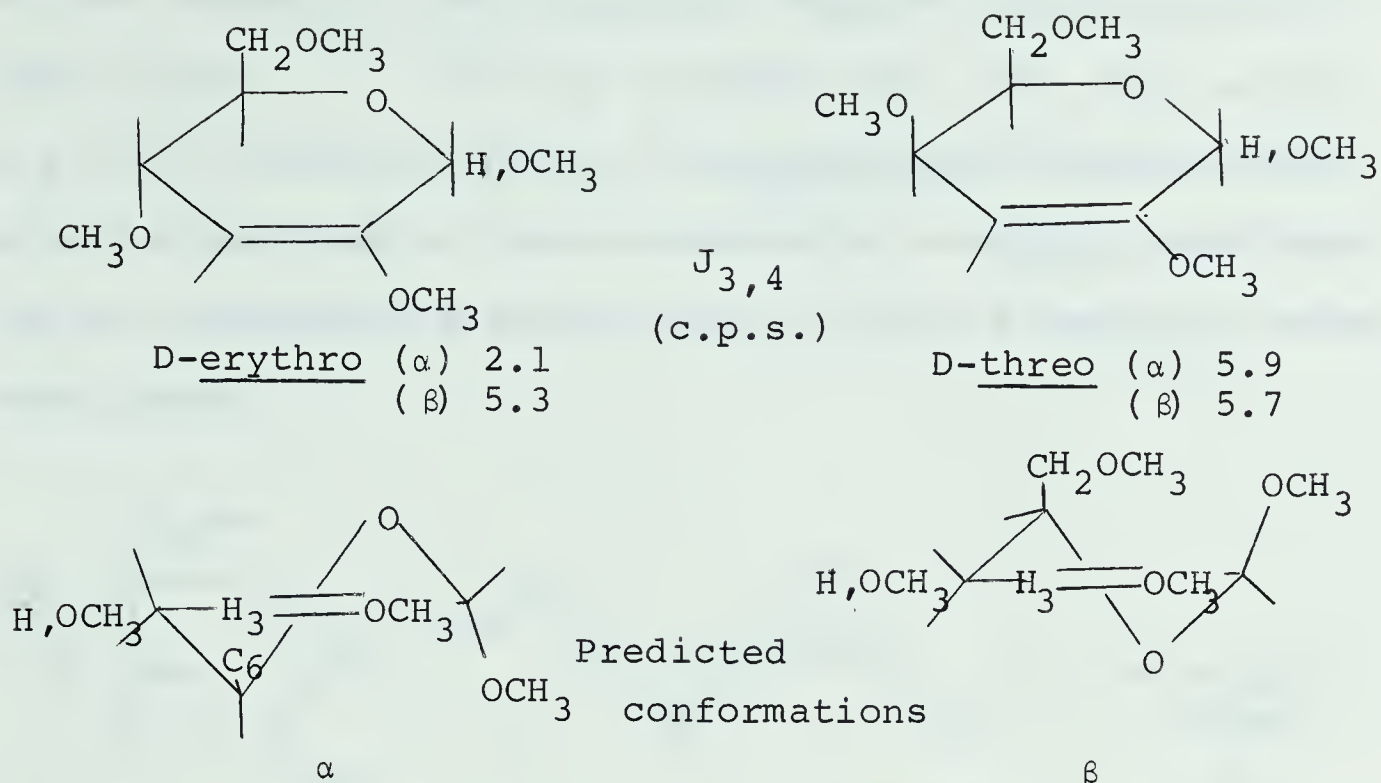
Of the eight glycals with a proton at C-2, five (see Table X) had observable $J_{2,4}$ coupling constants. Two

glycals, V and VIII, have conformations that provide a planar "W" system from H₂ to H₄. These have relatively large J_{2,4} values (1.3 - 1.5 c.p.s.). In the compounds I to IV, VI and VII, the planar "W" is not present but medium J_{2,4} values (0.5 - 0.8 c.p.s.) are observed in the flattened systems IV, VI and VII. For compounds I, II and III which are not flattened, J_{2,4} was near zero. Small J_{1,5} values are sometimes seen, but no significant data was obtained.

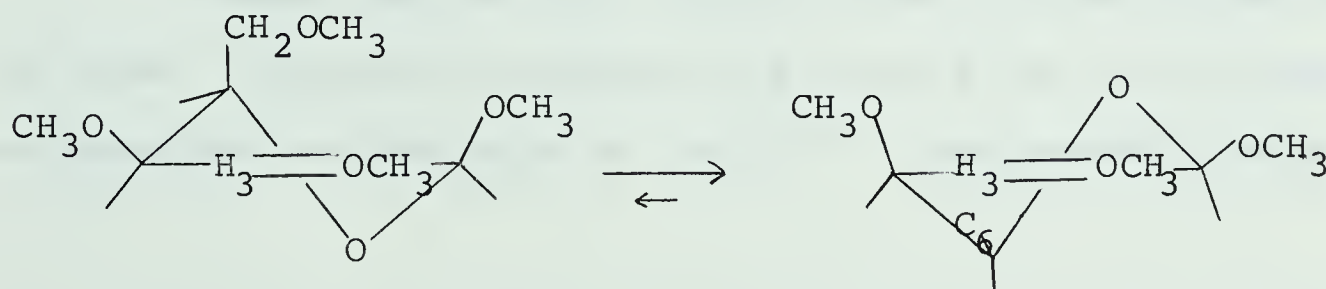
Large J_{3,5} couplings (1.5 - 1.9 c.p.s.) were seen where the conformations provided the planar "W" geometry, i.e. in VIII, XIII, XIV and XVI, and intermediate values (0.5 - 0.9 c.p.s.) were observed where this geometry could not be present but where the two C-H bonds were approximately parallel, i.e. in IV, VI, VII and IX to XII. Those compounds wherein neither of these criteria could be satisfied were found to have J_{3,5} values near zero, i.e. I, II, III and V.

Ferrier, Overend and Sankey (121) have used the previously discussed distinct P.M.R. parameter patterns for the assignment of anomeric configuration. The present work provides a logical basis for such assignments and, on the basis of a realistically-sized A^(1,2) effect, it should be possible to predict the conformation in any similar system. A case in point is the group of four methyl 3-deoxy-2,4,6-tri-O-methyl-D-hex-2-enopyranosides examined by E.F.L.J. Anet (112).

Solely on the basis of the A^(1,2) effect, it can be predicted that the α-anomers have the H1 conformation and the

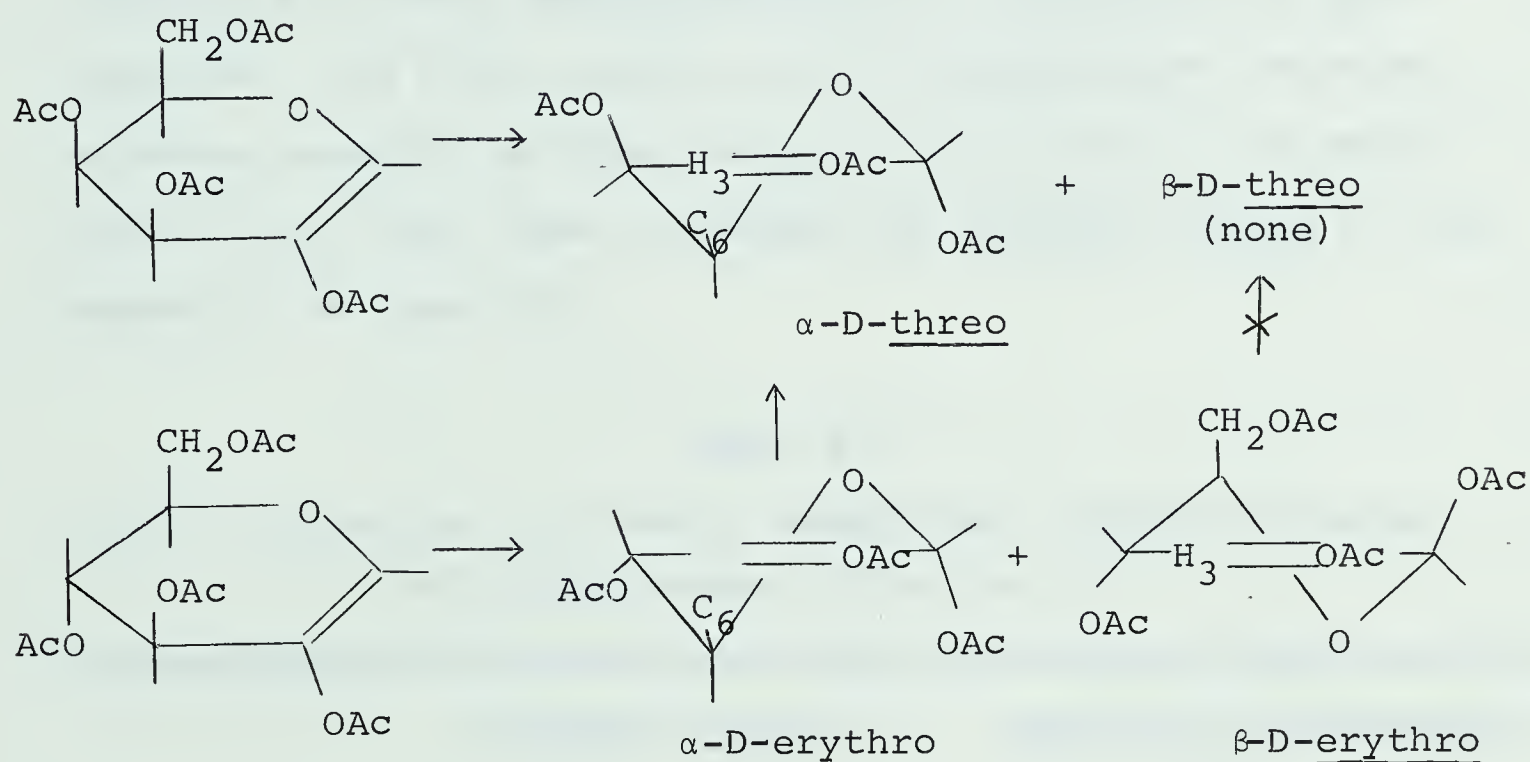


β -anomers have the 1H conformation. The $J_{3,4}$ splittings, except that for β -D-threo, confirm this prediction. In the one exception, the three substituents not in the olefinic plane were all cis. This suggests that the interactions here were greater than the total $A^{(1,2)}$ and anomeric effects and so another conformation was adopted.



The reaction of 2-acetoxy-3,4,6-tri-O-acetyl-D-galactal with acetic acid to yield acetyl 2,4,6-tri-O-acetyl-3-deoxy-D-threo-hex-2-enopyranosides has been investigated (120). Although similar reactions with the D-glucal (121, 122) and D-xylal (124) analogues have produced moderate yields

of the β -product, the D-galactal compound yielded none of this anomer. It was observed (121, 122) that acetyl 2,4,6-tri-O-acetyl-3-deoxy- α -D-erythro-hex-2-enopyranoside slowly epimerised to the corresponding α -D-threo enantiomer, but no corresponding epimerisation of the β -D-erythro anomer took place.



These observations indicate that in some situations, the other conformation-determining factors can be at least as important as the total of the $A^{(1,2)}$ and anomeric effects.

2. The Reaction of Acetylated Glycals with Nitrosyl Chloride.

Nitrosyl chloride formed cis-addition products (13, 16) with acetylated D-glucal (VI), D-galactal (V) and D-xylal (VIII). The P.M.R. parameters of these products are presented in Table XII. The high isolated yields (~90%) indicate that some specific mechanism is operative in this reaction. The P.M.R. spectra of the concentrated reaction mixtures revealed no other signals than those of the stated products, so that these compounds are probably formed to the extent of at least 95%.

TABLE XII

P.M.R. Parameters for Dimeric Acetylated 2-deoxy-2-nitroso- α -D-aldopyranosyl Chlorides. ^a

	<u>Chemical Shifts (τ)</u>			<u>Coupling Constants(c.p.s.)</u>		
	H ₁	H ₂	H ₃	J _{1,2}	J _{2,3}	J _{3,4}
<u>Gluc</u> (XVII)	3.33	4.54	3.95	3.5	9.0	9.5
<u>Galact</u> (XVIII)	3.31	4.47	4.08	3.7	11.1	3.6
<u>Xylo</u> (XIX)	3.39	4.62	3.98	3.8	11.0	9.8

^a. Determined at 60 Mc.p.s. in deuteriochloroform solution.

The halogenations and halogenomethoxylations of V, VI and 3,4-dihydropyran (14) provided evidence for the mechanism of additions to glycals. The cis and trans additions of nitrosyl chloride to norbornenes and Δ^9 -octalin, respectively, observed by Meinwald et al., (15) did not provide enough data

to allow definite selection of a mechanism. However, an attractive explanation is one in which a single mechanism does accommodate both cis and trans additions.

The first step involves production of an 'onium ion, with the cyclic contributing structure being the most important. Then the aptitude of the intermediate to being opened cis or trans controls the stereochemistry of the product. The clean reactions with some norbornenes (15) where rearrangements or cyclizations were especially favorable, indicates that very little carbonium ion character is developed in this reaction.

A kinetic study (125) of alkene-nitrosyl chloride reactions has not elucidated the mechanism of addition. However, the present reaction is readily explained by extension of a mechanism advanced for the high proportion of cis chlorination of V and VI (14).

The initial reaction of the nitroso function may be stereoelectronically controlled by the participation of the lone-pairs of the ring oxygen or sterically controlled by the 3-acetoxy function. The oxocarbenium ion of the intermediate is then most readily attacked through paths that allow the participation of the lone-pairs of the ring oxygen. Participation by one lone-pair requires a skew-boat conformation, while participation of the other lone-pair requires a chair-formed ring (see Figure 31). This combination of conformational energy and stereoelectronic control readily explains the stereospecific cis addition of chlorine and nitrosyl chloride to V and VI.

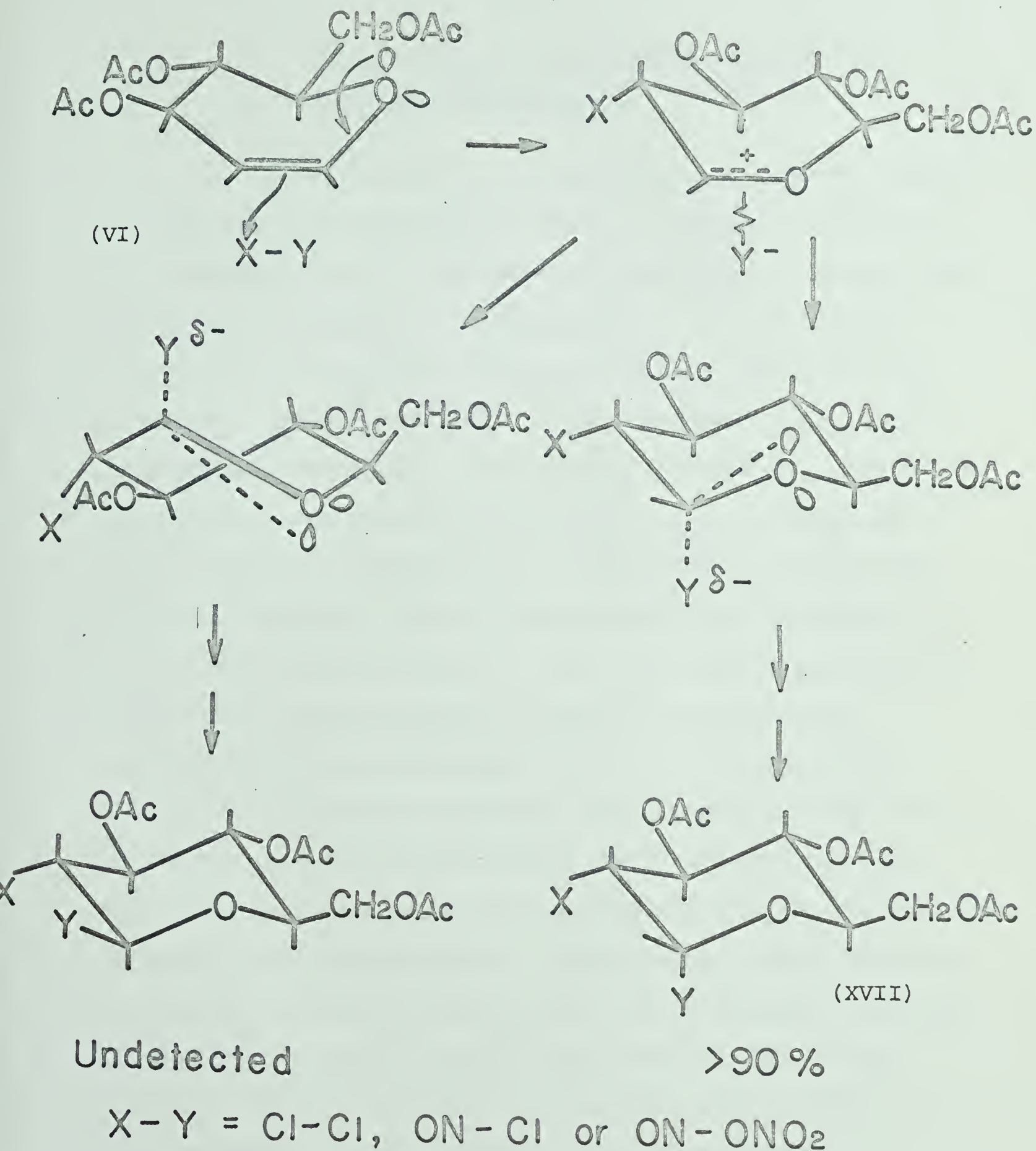
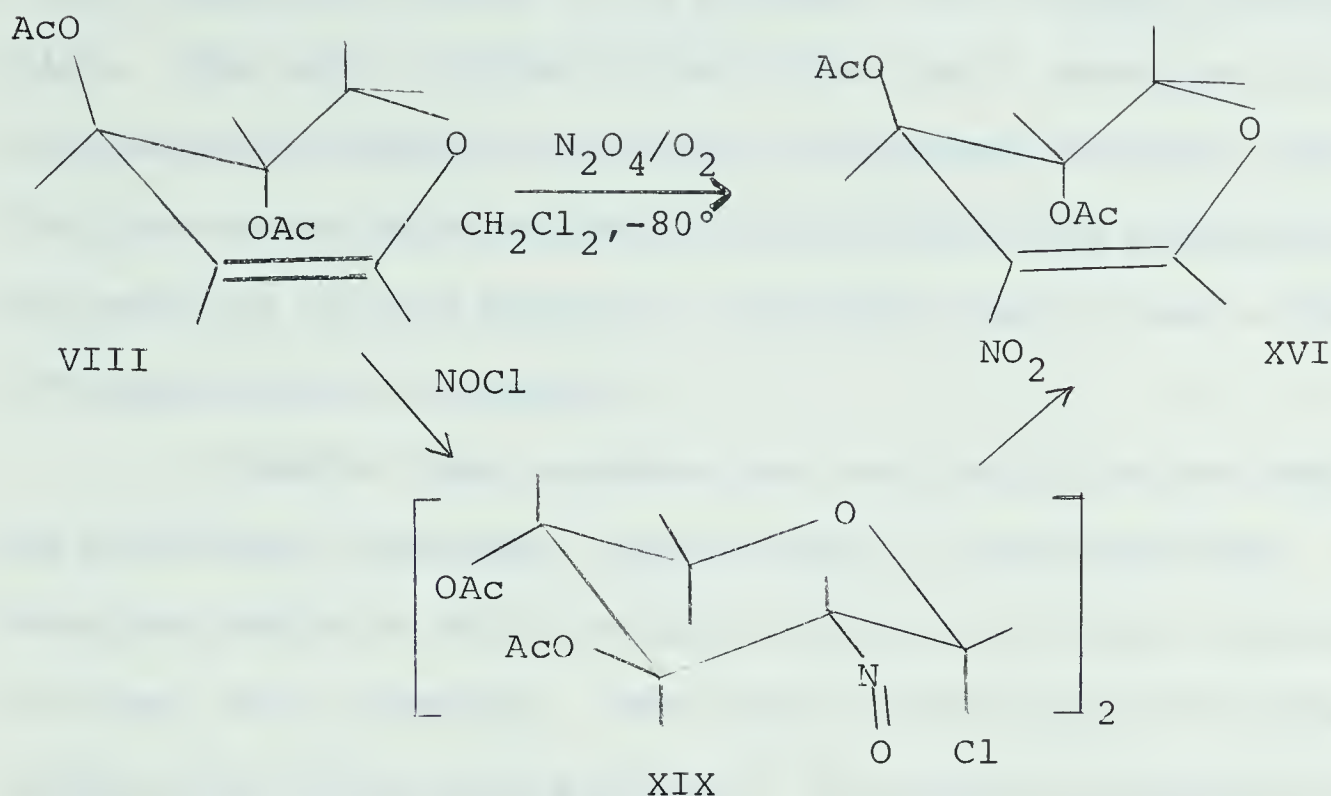


FIG. 31. The stereochemical route of the reaction of 3,4,6-tri-O-acetyl-D-glucal (VI) with strongly electrophilic reagents.

3. The Reaction of Acetylated Glycals with Dinitrogen Tetroxide.

As mentioned in the Introduction, alkenes react with dinitrogen tetroxide to yield a variety of products. The evidence for the structure of dinitrogen tetroxide was reviewed in relation to its reactions. In the present research, two different products could be found and the relative proportions of these were dependent upon solvent, temperature and several other factors (Table I). The series of hitherto unknown nitroglycals was first encountered in the decomposition of 3,4-di-O-acetyl-2-deoxy-2-nitroso- α -D-xylosyl chloride (XIX) which provided, in low yield, 3,4-di-O-acetyl-2-nitro-D-xylal (XVI). The possibility of XVI having the corresponding nitrosoxylal structure was eliminated by the observation that it was a colorless crystalline compound that formed colorless solutions and had the approximate molecular weight for the monomeric form. The nitroxylal structure also agreed better with the results of the elementary analyses. Investigation of the reaction of 3,4-di-O-acetyl-D-xylal (VIII) with dinitrogen tetroxide showed that a similar product was given in high yield.

Initial attempts to react XVI with methanol led to a final product containing one acetoxy and two methoxy groups. This work is described in Section 4 of this Discussion.



Reaction at -80° in methylene chloride of dinitrogen tetroxide with 3,4,6-tri-O-acetyl-D-galactal (V), 3,4,6-tri-O-acetyl-D-glucal (VI) and 4,6-di-O-acetyl-3-O-methyl-D-glucal (VII), gave syrupy products with P.M.R. spectra (Table X) and I.R. spectra very similar to those of XVI. These products were often obtained impure (as shown by P.M.R. spectroscopy). Since attempts to purify them failed, the reaction of dinitrogen tetroxide with glycals was studied to discover the sources of by-products.

In view of the foregoing remarks on the structure of dinitrogen tetroxide and the experience of White and Feldman (41), the effects of temperature and solvent on the reaction were examined. In diethyl ether at 0° , VI gave a mixture of the expected 3,4,6-tri-O-acetyl-2-nitro-D-glucal (XIII) and an unknown blue-white crystalline material. This latter product was obtained in a yield of approximately 40%, and its

P.M.R. spectrum showed it to possess the α -D-gluco configuration. The great similarity with the P.M.R. spectrum of 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucosyl chloride (XVII) and the blue-green colours present during both the production and the melting of this material, suggested that it was a dimeric 2-deoxy-2-nitroso compound.

Whether this compound had resulted from the addition of dinitrogen tetroxide and was thus a nitrosonitrate, or from the addition of dinitrogen trioxide giving a nitroso-nitrite, was uncertain. Additions of dinitrogen trioxide to alkenes had often been performed (19), whereas nitrosonitrates were of uncertain existence as previously mentioned in the Introduction. I.R. spectroscopy was of no assistance since the strong broad absorption at 1680 cm^{-1} could equally well have been produced by a nitrate or a nitrite ester (126), and the absorption pattern below 1500 cm^{-1} was too complex to allow a definite decision. During the examination of the crystalline material, it was found to decompose readily to the 2-nitroglycal XIII. This observation shed doubt on the proportion of the unidentified material produced at 0° in ether solvent. It also raised the possibility that XIII, and its analogues, were produced by decomposition of intermediate compounds of this type.

The first step in the investigation was to determine the effect of the presence of other nitrogen oxides on these reactions. Dinitrogen trioxide (b.p. 3.5°) is an unstable gas at room temperature which decomposes into nitric oxide and nitrogen dioxide.



The gas was allowed to distil from a lecture bottle and admixed with nitric oxide before condensation in methylene chloride at approximately -80° . Nitric oxide (b.p. -152°) was continuously bubbled through the intensely blue solution to suppress the decomposition of the dinitrogen trioxide. Tri-O-acetyl-D-glucal (VI) was added as a solution in methylene chloride and, after work-up of the reaction mixture, a brown syrup remained. The P.M.R. spectrum contained a few very broad peaks in the region τ 4 to 6, together with a broad signal for acetyl group but nothing recognizable could be seen. The I.R. spectrum contained several broad absorptions in the region $1500\text{--}1700\text{ cm}^{-1}$, but again nothing that was recognizable. On storage, this product evolved oxides of nitrogen and, even after six months, no well-defined or recognizable spectra could be obtained.

Dinitrogen pentoxide was produced by the action of fuming nitric acid on phosphorus pentoxide (104) in a stream of oxygen. The unstable dinitrogen pentoxide (b.p. 47°) was condensed in methylene chloride at approximately -80° in the presence of a stream of oxygen. Then a solution of VI was added to this dinitrogen pentoxide solution. As shown by P.M.R. spectroscopy, the isolated material contained approximately 30% of the nitroglycal XIII as well as a number of saturated compounds. (Possibly most of the XIII present was produced by dinitrogen tetroxide present in the dinitrogen pentoxide since ozone was not used

in the preparation of dinitrogen pentoxide as recommended). This product evolved nitrogen oxides at room temperature and, when heated in vacuo, the proportion of XIII increased. When treated with pyridine in benzene, the product yielded XIII and some pyridinium salts were precipitated. However, it was found that complete separation of these salts from XIII was very difficult.

Thus it was concluded that the presence of dinitrogen trioxide had to be eliminated but without including large amounts of dinitrogen pentoxide in the gas stream. When an approximately equimolar stream of dinitrogen tetroxide and oxygen was condensed in methylene chloride at approximately -80° , or in diethyl ether at approximately 0° , colorless solutions were produced. When no oxygen was used, blue solutions resulted and these could then be slowly decolorised by the passage of oxygen through them.

The acetylated glycals, V - VIII, were reacted with dinitrogen tetroxide and oxygen in ether at 0° and the products isolated by precipitation. The reactions were performed in diethyl ether, from which much of the product precipitated. After the reactions had finished, enough methylene chloride was added to just dissolve the precipitates and then the reaction solutions were added to excess cold n-hexane, and the products usually precipitated as fine needles. The product of reaction with 3,4-di-O-acetyl-D-xylal (VIII) was very unstable and, in the one case when a few crystals were deposited on the walls of the reaction

flask, these immediately decomposed upon reaching room temperature. The yields of these products from V, VI and VII were 58, 91, and 51% respectively, on the basis of nitroso-nitrate. These products were unstable, as mentioned previously. Their decomposition appeared to be autocatalytic, since samples could be stored several months when spread out in Petrie dishes in vacuo over potassium hydroxide and phosphorus pentoxide, but slowly decomposed to XIII when placed in a closed flask under dry conditions, or when dissolved for spectroscopic analysis.

Samples which were carefully protected from heat until the actual moment of combustion had the correct analysis for dinitrogen tetroxide addition compounds, as now expected since dinitrogen trioxide had been eliminated from the gas stream. These substances had the approximate molecular weights for the dimeric forms. Furthermore, the addition compound with 3,4,6-tri-O-acetyl-D-glucal (VI) reacted with acetic anhydride and triethylamine at -5° to give a 93% yield of penta-O-acetyl-2-oximino-D-glucopyranoside (XXIII) which had P.M.R. and I.R. spectra indistinguishable from those of the analogous nitrosyl chloride addition compound XVII (10). A similar reaction occurred with acetic anhydride and anhydrous sodium acetate and, in this case, the inorganic salts (sodium acetate and sodium nitrate/nitrite) were recovered upon dilution of the reaction mixture with diethyl ether. This inorganic mixture gave a negative test for nitrite (no iodine produced from acidified aqueous potassium iodide) and a positive test for nitrate (intense blue coloration with diphenylamine in 98% H_2SO_4) (102).

TABLE XIII

P.M.R. Parameters of Some Acetylated 2-Deoxy-2-nitroso- α -D-hexopyranosylNitrates a

a) Chemical Shifts (τ).	H ₁	H ₂	H ₃	H ₄	H ₅ , 2H ₆	Acetates	-OCH ₃
<u>Glucob</u> (XX)	3.23	4.49	4.06	4.80	5.5 - 6.0	7.93 7.95 8.01	-
<u>3-O-Me gluco</u> (XXI)	3.36	4.61	~ 5.9	4.80	5.5 - 6.2	7.85 7.92	6.53
<u>Galacto</u> (XXII)	3.26	(4.0 - 5.0) ^c			5.5 - 6.3	7.84 7.98 8.02	-
133							
b) Coupling Constants (c.p.s.)	J _{1,2}	J _{2,3}	J _{3,4}	J _{4,5}			
<u>XXb</u>	4.2	11.1	9.4	10.3			
XXI	4.3	10.5	9 - 10	9 - 10			
XXII	3.7	(- - -	c)			

a. Recorded at 60 Mc.p.s. as 20% w/v deuteriochloroform solutions at 35+2°, unless otherwise stated.b. Recorded at 100 Mc.p.s.c. Non-first-order multiplet.

Thus it was concluded that these crystalline compounds were 2-deoxy-2-nitrosonitrates.

Crystalline 3,4,6-tri-O-acetyl-2-deoxy-2-nitroso- α -D-glucosyl nitrate (XX) was placed in the conditions in which XIII had been produced to examine the possibility that XX was an intermediate in the formation of XIII. A solution of XX was subjected to reaction with $\text{N}_2\text{O}_4\text{-O}_2$ and the solution concentrated. Evaporation from the product of several portions of dry carbon tetrachloride in vacuo at 50° was made before examination of the product by P.M.R. spectroscopy. Only small amounts of XIII were produced. Thus compound XX essentially survived the conditions used for preparing XIII, and was not an intermediate in the formation of XIII.

An attempt to prepare XX from the corresponding nitrosyl chloride adduct of tri-O-acetyl-D-glucal by reaction with silver nitrate in acetonitrile led to the formation of the nitroolefin XIII. When the reaction mixture was examined before completion, only the starting material, XVII, and the nitroolefin, XIII, were present.

Except for XIV, the acetylated 2-nitroglycals were prepared by passage of dinitrogen tetroxide and oxygen into a stirred methylene chloride solution of the acetylated glycal at approximately -80° . The reaction mixtures were then concentrated and any nitrosonitrate present was decomposed by repeatedly evaporating carbon tetrachloride from the residue. The carbon tetrachloride itself was found to adhere tenaciously and prolonged warming in vacuo

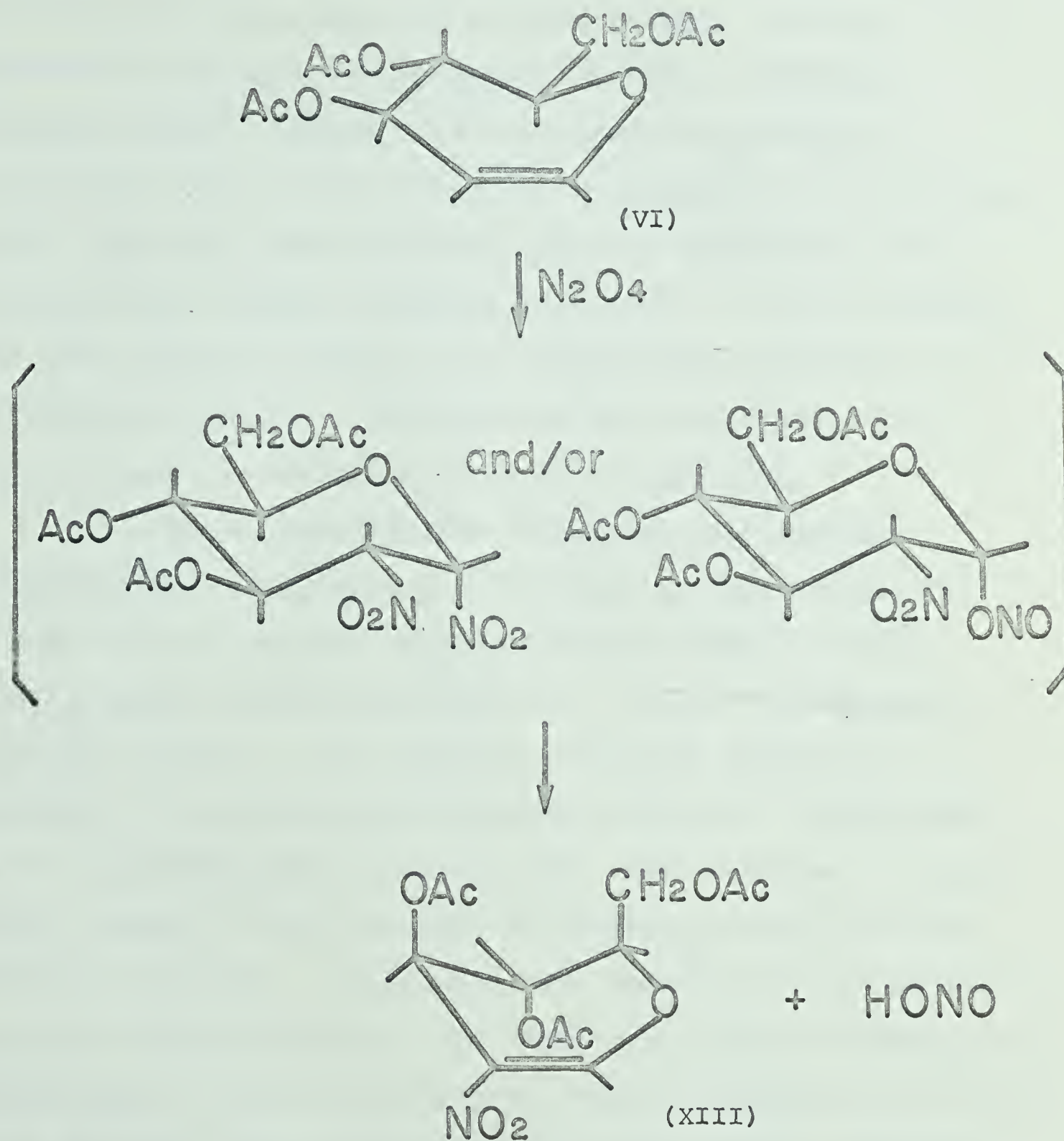


FIG. 32. The postulated reaction mechanism for the formation of 3,4,6-tri-O-acetyl-2-nitro-D-glucal (XIII).

was required for complete removal. Near-quantitative yields of XIII and XV were obtained in this fashion. XVI was purified by sublimation in vacuo, leaving an oligomeric residue behind. However, 4,6-di-O-acetyl-3-O-methyl-D-glucal was found to yield only the corresponding nitrosonitrate (XXI) under the above described reaction conditions, and XIV resulted only through decomposition of XXI. For this purpose, XXI was prepared in ether at 0° and the crude product allowed to decompose slowly. The resulting XIV was shown by P.M.R. spectroscopy to contain only traces of impurities.

A brief investigation showed that the reaction producing the nitroglycal XIII behaved, to some extent, as a free radical reaction competing with the ionic reaction that produced the nitrosonitrate XX. At -80° in methylene chloride (Table I), the formation of XX was favored by the presence of tetrachlorohydroquinone (inhibitor) and by added salt (tetramethylammonium chloride). The influence of light and/or oxygen on the reactions was somewhat smaller and not readily explained. Occasionally the reaction at -80° failed and only starting material was recovered. The main experimental difficulty in these investigations was the decomposition of XX to XIII and this led to uncertainties in the results and their interpretation.

As shown in Fig. 32, the production of nitroglycals can be regarded as addition followed by elimination. That the production of the nitroglycals involves a radical process is indicated by a) the failure to ever observe the $\overset{\oplus}{\text{NO}}_2 \overset{\oplus}{\text{NO}}_2$

ionization of dinitrogen tetroxide (25), and b) the previous observations that nitro-containing products of these reactions arise from free-radical processes (18, 19). "Molecule-induced homolytic decomposition" (127), i.e. attack by a C=C function to produce homolysis of a susceptible bond, has been found for the peroxide linkage. Similar homolyses have been found for F-F (128), Cl-Cl (129, 130) and possibly for the I-I (131) bonds. A consideration of the energy changes for each step, including that for addition of Cl· to alkene (132), indicated to Poutsma (131) that "molecule-induced homolytic decomposition" of chlorine is a favorable process for initiation of chain-reactions. Cage recombination of the induced radicals should yield an extremely small fraction of the observed products. In any case, it would be difficult to decide whether the addition product is derived from a concerted addition or from cage recombination. E.S.R. measurements (133) have shown that nitrogen dioxide forms a charge-transfer complex with olefins. Such a complex may be a precursor to the production of the first radical species.

The cis-addition of nitrosyl nitrate in diethyl ether is taken to be similar to the cis-addition of chlorine (14) and nitrosyl chloride to acetylated glycals, since diethyl ether probably selectively solvates the nitrosyl nitrate isomer of dinitrogen tetroxide as mentioned in the Introduction. That VII forms the nitrosonitrate under all conditions is indicative of some effect involving the methyl ether function adjacent to the reaction site.

4. The Reaction of 3,4-Di-O-acetyl-2-nitro-D-xylal (XVI) with Methanol.

Nitroolefins are highly susceptible to nucleophilic attack (78) and many publications have been made on this subject. Of the several acetylated nitroglycals available, 3,4-di-O-acetyl-2-nitro-D-xylal (XVI) was the only one that was crystalline. For reasons of purity and ease of handling, this compound was used to establish the general mode of reaction of the nitroglycals with alcohols. A similar, but shorter, study of the analogous reactions of syrupy 3,4,6-tri-O-acetyl-2-nitro-D-glucal (XIII) was then made and is reported in the following section of this Discussion.

Compound XVI was found to react readily with methanol and other nucleophilic reagents and a kinetic examination showed these reactions to be base-catalysed. The initial reaction of XVI with methanol involved an allylic rearrangement and loss of the 3-acetoxy to produce a 2,3-unsaturated compound XXIV, a quite common reaction for 1,2-glycals (134). Further reactions led to an isomer of XXIV, compound XXV, and then to compounds XXVI and XXVII containing one acetoxy and two methoxy groups. The P.M.R. and I.R. spectra of these compounds are reported in Tables XIV and XV. The rates of these processes could not always be duplicated.

Reaction of XVI with methanol containing triethylamine was found to rapidly form, in near quantitative yield,

TABLE XIV

The P.M.R. Parameters of Compounds Formed in the Reaction
of XVI with Methanol

(a) Chemical Shifts^a (τ).

Compound	H ₁	H ₂	H ₃	H ₄	H _{5e} ^d	H _{5a}	OCH ₃	OAc
XVI ^b	1.61	-	4.02	4.90	5.46	5.92	-	two at 7.89
XXIV	4.49	-	2.76	4.70	5.84	6.12	6.46	7.88
XXV	1.78	-	5.62	4.91	5.59	5.90	6.43	7.93
XXVI	4.72	5.40	5.87	4.95	5.92	6.42	6.46	7.89
XXVII	5.28	5.67	5.95	5.10	5.87	6.69	6.51	7.90

(b) Coupling constants^a (c.p.s.)

Compound	J _{1,2}	J _{2,3}	J _{3,4}	J _{4,5e}	J _{4,5a}	Others
XVI ^b	-	-	3.0	2.1 ^c	1.5 ^c	J _{1,5a} ~ 0.9 ^c , J _{3,5e} 1.8 ^c , J _{3,5a} 0.6 ^c .
XXIV	-	-	5.6 ^c	3.2	1.0 ^c	J _{1,5a} ~ 0.5, J _{1,3} ~ 0, J _{3,5a} 1.3 ^c .
XXV	-	-	~ 1.9 ^c	~ 1.9 ^c	2.7 ^c	J _{1,3} or J _{1,5a} 0.7 ^c J _{3,5e} ~ 1.9, J _{3,5a} 0.7.
XXVI	3.9 ^c	4.1 ^c	4.1 ^c	1.9 ^c	2.2 ^c	J _{1,3} and/or J _{1,5e} ~ 0.7 ^c , J _{3,5a} 1.3.
XXVII	7.7 ^c	9.9	8.7	5.6	9.5	11.7

a. Determined at 100 Mc.p.s. at 35±2° with 20% w/v CDCl₃ solutions.

b. Previously reported (13) at 60 Mc.p.s. for a 20% w/v CDCl₃ solution.

c. Demonstrated by double irradiation.

d. H_{5e} assigned to the lower-field H₅ (135).

TABLE XV

Infra-Red Absorptions (cm^{-1}) of Compounds Involved in the Reaction of
XVI with Methanol.

	XVI	XXIV	XXV	XXVI	XXVII
Alkene $\text{C}=\text{C}_{\text{H}}$ stretch	$\sim 3090\text{w}$	$\sim 3090\text{w}$	$\sim 3090\text{w}$	—	—
Methoxy C-H stretch	—	$\sim 2840\text{m}$	$\sim 2840\text{m}$	$\sim 2840\text{m}$	$\sim 2840\text{m}$
Acetoxy C=O stretch	Strong, broad absorption, 1740 - 1750, for all.				
Alkene C=C stretch	1643s	1682w	1643s	—	—
Nitro asymmetric stretch	1509s	1538s	1511s	1560s	1563s
Nitro symmetric stretch	1350s	1354s	1350s	$\sim 1372\text{m}$	$\sim 1372\text{m}$
Alkene $\text{C}=\text{C}_{\text{H}}$ out of plane	$\sim 820\text{m}$	$\sim 820\text{m}$	$\sim 820\text{m}$	—	—

w, m, s = weak, medium or strong absorptions.

crystalline methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-xyloside (XXVII). This structure was assigned on the basis of the elementary analyses, I.R. (nitro group) and P.M.R. spectra (Fig. 33). The β -xylo configuration was clearly evident from the coupling constants listed in Table XIV which require axial orientations for the protons at the 1,2,3 and 4 positions, and one diaxial coupling interaction between H₄ and a proton at C-5. The lowest-field signal is that for H₄, indicating that the acetoxy function is located at C-4. The formation of XXVII from XVI was obviously a multi-stage process. In order to establish the nature of the overall reaction, a study of the much slower uncatalysed reaction of XVI with methanol was undertaken.

The course of the optical rotatory change which occurred when XVI was treated with methanol was determined for the conditions reported in Fig. 36. As seen in Fig. 36, there was an initial rapid increase in rotation followed by a slower decrease and this was followed by a slow increase over a long period of time. It was decided to interrupt the reaction when the rotation of the reaction mixture approached its maximum value. As seen in Fig. 34, which is the P.M.R. spectrum of Run 1a (1.9 hr reaction time, Table XVI), the syrupy product was a mixture containing a high concentration of a new compound XXIV considered to be the first isolable product. Much smaller amounts of XVI and another compound XXV (singlet at τ 1.82) were also present. On storage, the syrup deposited a crystalline substance which was



FIG. 33. P.M.R. spectrum (100 Mc.p.s.) of methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro-β-D-xyloside (XXVII). (DISCUSSION, Section 4).

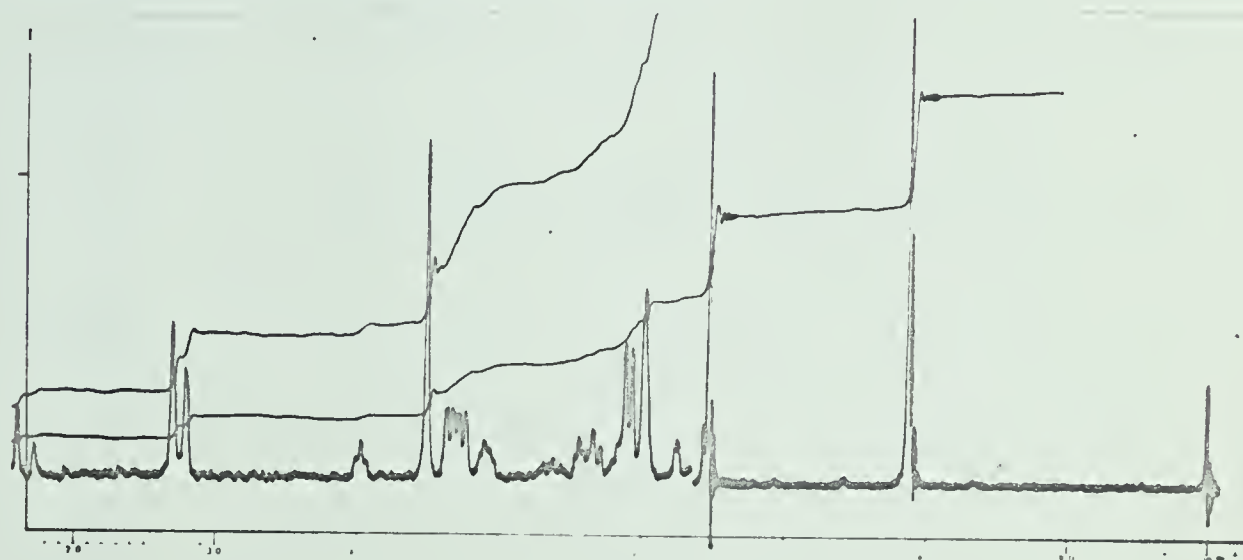


FIG. 34. P.M.R. spectrum (60 Mc.p.s.) of the sample from the reaction of XVI with methanol (Run 1a, reaction time 1.9 hr). (DISCUSSION, Section 4).

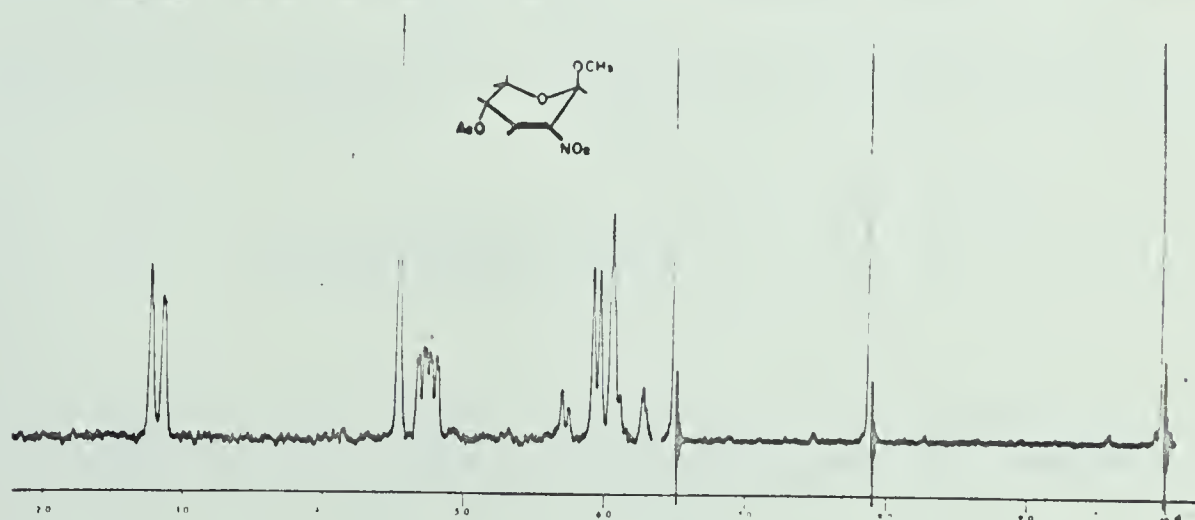


FIG. 35. P.M.R. spectrum (60 Mc.p.s.) of methyl 4-O-acetyl-2,3-dideoxy-2-nitro-β-D-glycero-pent-2-enopyranoside (XXIV). (DISCUSSION, Section 4).

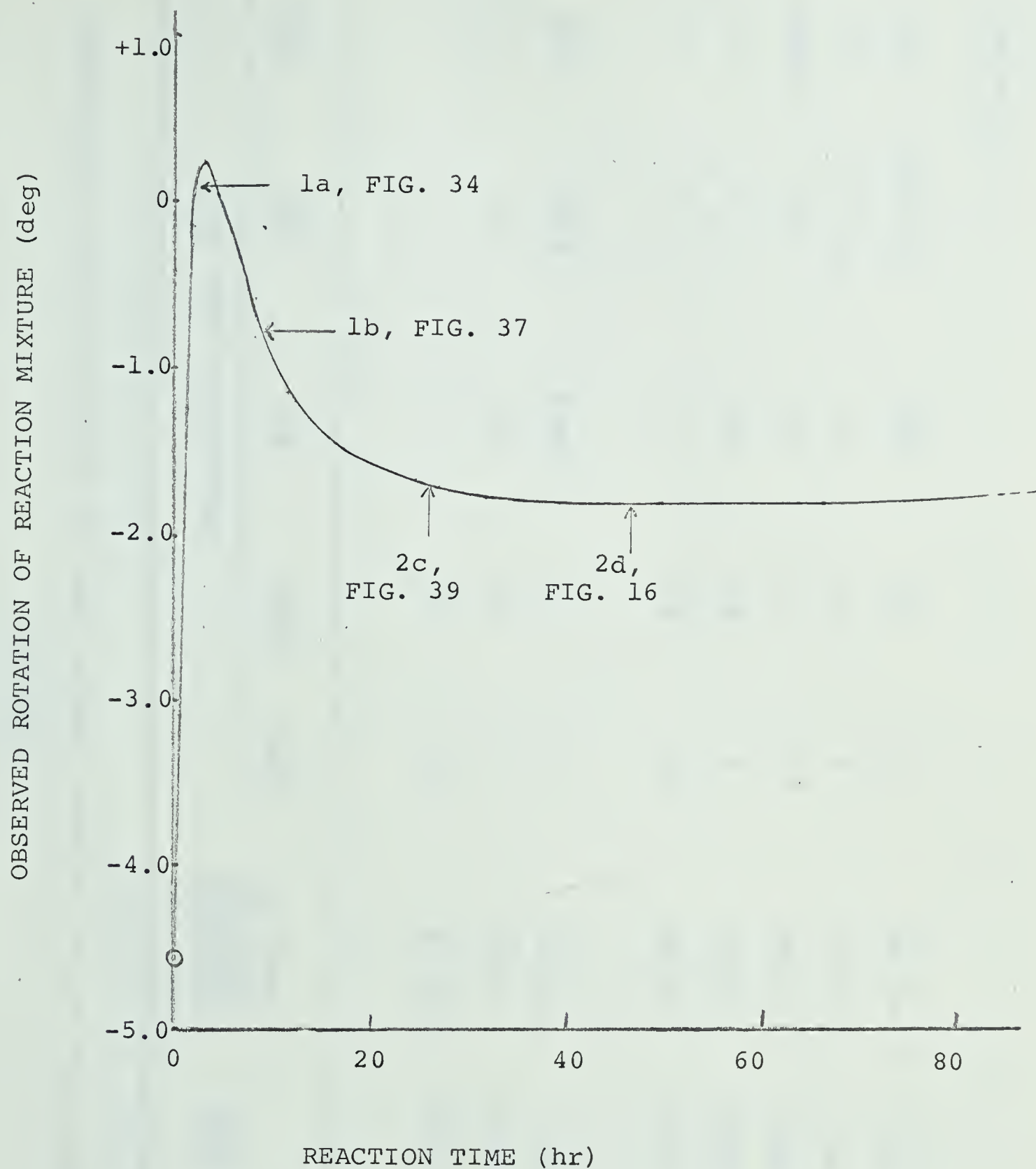


FIG. 36. The observed rotation (10 cm tube) of 0.0648M 3,4-di-O-acetyl-2-nitro-D-xylal (XVI) in 75% MeOH and 25% benzene (v/v) at 26°. First and second runs (Table XVI).

TABLE XVI

The Compositions of the Isolated Samples from the Reaction of XVI with Methanol

Run	Time (hr)	Observed Rotation (deg) ^a <u>—</u>	Composition (mole %) ^b <u>—</u>			
			<u>XVI</u>	<u>XXIV</u>	<u>XXV</u>	<u>XXVI</u> <u>XXVII</u>
<u>First</u>						
1a ^c	1.90	+0.04	14	79	7	0 0
1b	8.60	-0.66	0	40	30	30 0
1c ^c	330	-0.85	0	0	trace	43+2 57+2
<u>Second</u>						
2a	1.20	-0.66	25	69	6	0 0
2b	4.80	+0.09	0	65	29	6 0
2c	25.6	-1.62	0	9	26	65 trace
2d	46.8	-1.74	0	5	15	70 to 75 ≤10
2e ^c	70.7	-1.76	0	≤2	15+2	75 to 85 ≤10
(-Cont'd-)						

(-Cont'd-)

TABLE XVI
(-Cont'd-)

Run	Time (hr)	Observed Rotation (deg) ^a	Composition (mole %) ^b				
			<u>XVI</u>	<u>XXIV</u>	<u>XXV</u>	<u>XXVI</u>	<u>XXVII</u>
<u>Third</u>							
3a	0.53	-2.00	62	38	0	0	0
3b	3.20	+0.22	4	72	24	0	0
3c ^c	76.7	-1.21	0	15	68	17	trace
3d	97.9	-1.23	0	15	64	21	trace
3e	145	-1.21	0	14	57	19 to 29	≤10
3f	275	-1.17	0	8	44	33 to 38	10 to 15
3g	850	-1.12	0	4	16	57 ± 5	23 ± 5
3h	1330	—	0	0	14	56 ± 5	30 ± 5
3i	2500	—	0	0	8	54 ± 5	38 ± 5
<u>Fourth</u>							
4a	25.5	-1.45	0	15	55±5	30 ± 5	0
4b	88.4	-1.67	0	trace	19	70 ± 5	11 ± 5

(-Cont'd-)

TABLE XVI
(-Cont'd-)

<u>Run</u>	<u>Time</u> (hr)	<u>Observed</u> <u>Rotation</u> (deg) ^a	<u>Composition (mole %)</u> ^b			
			<u>XVI</u>	<u>XXIV</u>	<u>XXV</u>	<u>XXVI</u> <u>XXVII</u>
<u>Fifth</u>	5a	-1.10	0	22	67	11 0
	5b	93	0	18	63	16 to 19 ≤6
	5c	402	0	9	36	30 to 40 15 to 25
<u>Sixth</u>	6a	-1.26	0	19	66	10 to 15 ≤5
	6b	-1.21	0	15	48	27 to 37 ≤10
146						
<u>Seventh</u>	7	—	0	18	58	16 to 24 ≤8
	8	—	0	17	68	10 to 15 ≤5

a. For a 10 cm polarimeter tube.

b. Values for VIII, XXIV and XXV (errors approximately + 2%) are more precise than those for XXVI and XXVII. The sum, XXVI plus XXVII is precise, but the relative ratio of these two is not. As [XXVII] increases, the accuracy of this ratio decreases.

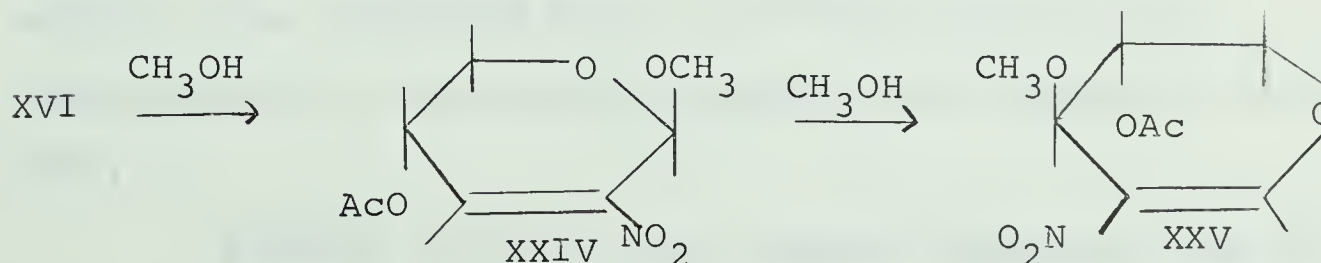
c. Also investigated by P.M.R. spectroscopy at 100 Mc.p.s.

purified by recrystallisation. Elemental analysis and the P.M.R. spectrum (Fig. 35) required the compound to have the composition $C_5H_5NO_4 (COCH_3) (OCH_3)$. Absorptions in the I.R. spectrum required the presence of an α, β -unsaturated nitro compound in which, for reasons of intensity and position of the C=C stretching frequency (136), a vinyl ether is absent. In the P.M.R. spectrum, the singlet at $\tau 4.49$ was assigned to the anomeric proton of a methyl pentoside as, in this system, only such a proton could be both sufficiently isolated and have this chemical shift. The chemical shift of the doublet at $\tau 2.76$ was then attributable to the olefinic nature of the 3-position, at which position a proton would have significant coupling with H_4 . The remaining signals were then readily assigned, and spin-spin decoupling used for confirmation.

It could be assumed that the formation of this compound did not involve configurational change at the 4-position and this is strongly supported by the β -xylo configuration of the end product of the reaction. The configuration of the anomeric center remained in doubt until it was discovered that reaction of compound XXIV with ethanol in the presence of triethylamine gave methyl 4-O-acetyl-2-deoxy-3-O-ethyl-2-nitro- β -D-xyloside (XXVIII) in a purity of at least 80% (Fig. 15). This configuration of XXVIII was required by the P.M.R. parameters which are very similar to those of XXVII (Fig. 33), which would be its 3-O-methyl analogue. Thus the aglycone cannot have been eliminated to any significant extent and the anomeric center was unaffected by this reaction.

Even if cage-effects had been operative under the reaction conditions, the large amount of retained methoxy function must indicate that readdition occurred from the same side as elimination and thus XXIV had the β -configuration. As will be seen later on the basis of the $A^{(1,2)}$ and anomeric effects, the conformation of XXVII can only be accommodated by a β -compound.

When the reaction of XVI with methanol was interrupted after 8.6 hr (Run 1b, Table XVI), the product isolated was clearly devoid of any XVI (Fig. 37). Besides 40 mole % of XXIV, there were 30 mole % each of two compounds, XXV and XXVI. In later runs, the concentration of XXV approached 70 mole % (Table XVI) thus making possible a close examination by P.M.R. spectroscopy. Both in coupling interactions and chemical shifts, the P.M.R. spectrum of XXV is closely related to those of compounds XIV and XVI (Table X). Of special significance are the very similar patterns of long-range coupling. Together with the positions and intensities of the double-bond and nitro asymmetric stretching absorptions (Table XV) in the infra-red region, which strongly suggest a 2-nitroglycal, this data was taken to indicate that XXV is 4-O-acetyl-3-O-methyl-2-nitro-D-xylal.



Assignment of the L-configuration to the 3-position was further supported when it was found that compounds XXVI and XXVII, which are the reaction products of XXV with methanol,

both have the L-configuration at this position. Reaction of 4,6-di-O-acetyl-3-O-methyl-2-nitro-D-glucal (XIV) with methanol (DISCUSSION, Section 5) yielded a product (XXXIII) with the β -gluco configuration, thus showing by analogy, that the reaction of XXV with methanol cannot affect the 3-position. Purification by chromatography gave, at best, an 85% pure sample of compound XXV. The P.M.R. spectrum of this sample is reproduced in Fig. 38.

As previously mentioned, the sample isolated from Run 1b contained 30 mole % of a compound XXVI. At longer reaction times, the concentration of this substance in isolated reaction samples increased to approximately 75 mole %.

P.M.R. spectroscopic examination of suitable samples (Runs 2c, 2d and 2e, Table XVI) showed them to have only weak characteristic very low-field signals and singlets of nitroglycals. Accordingly, when the infra-red spectra of samples rich in XXVI were examined (Fig. 40), only medium absorptions for α, β -unsaturated nitro compounds could be found, although strong absorption at about 1560 cm^{-1} was observed. This latter frequency is in a region characteristic for saturated nitro compounds (126). Attempts to isolate this substance were unsuccessful and it was characterised in admixture, chiefly, with compounds XXV and XXVII.

Signals in the P.M.R. spectra indicated that XXVI has one acetoxy and two methoxy functions and, together with the nitrogen content, formation from compound XXV and

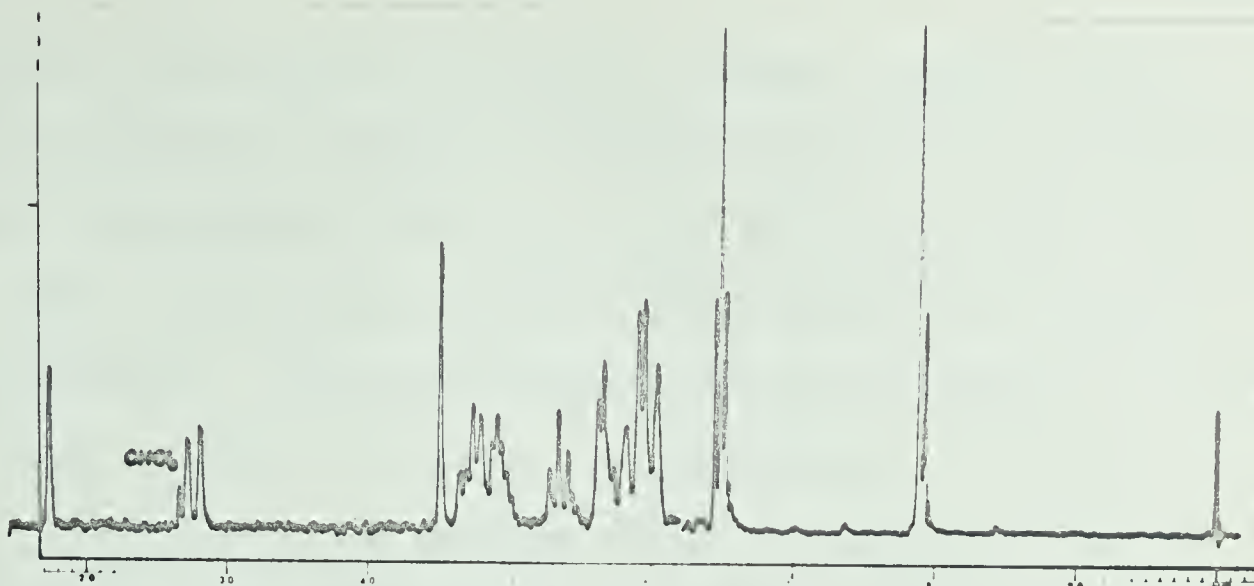


FIG. 37. P.M.R. spectrum (60 Mc.p.s.) of a sample from the reaction of XVI with methanol. (Run 1b, reaction time 8.60 hr). (DISCUSSION, Section 4).

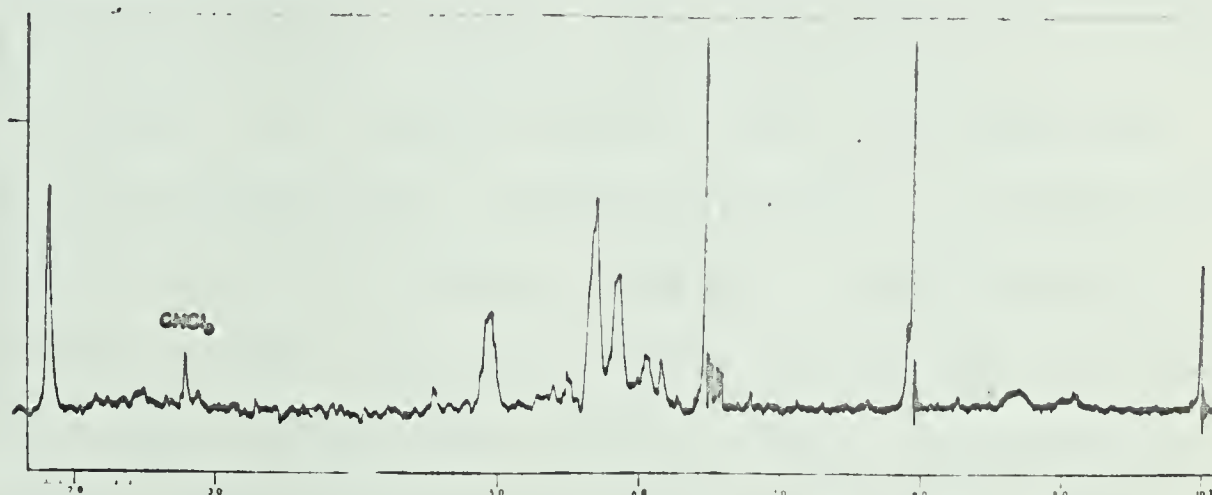


FIG. 38. P.M.R. spectrum (60 Mc.p.s.) of an 85% pure sample of 4-O-acetyl-3-O-methyl-2-nitro-D-xylal (XXV). (DISCUSSION, Section 4).

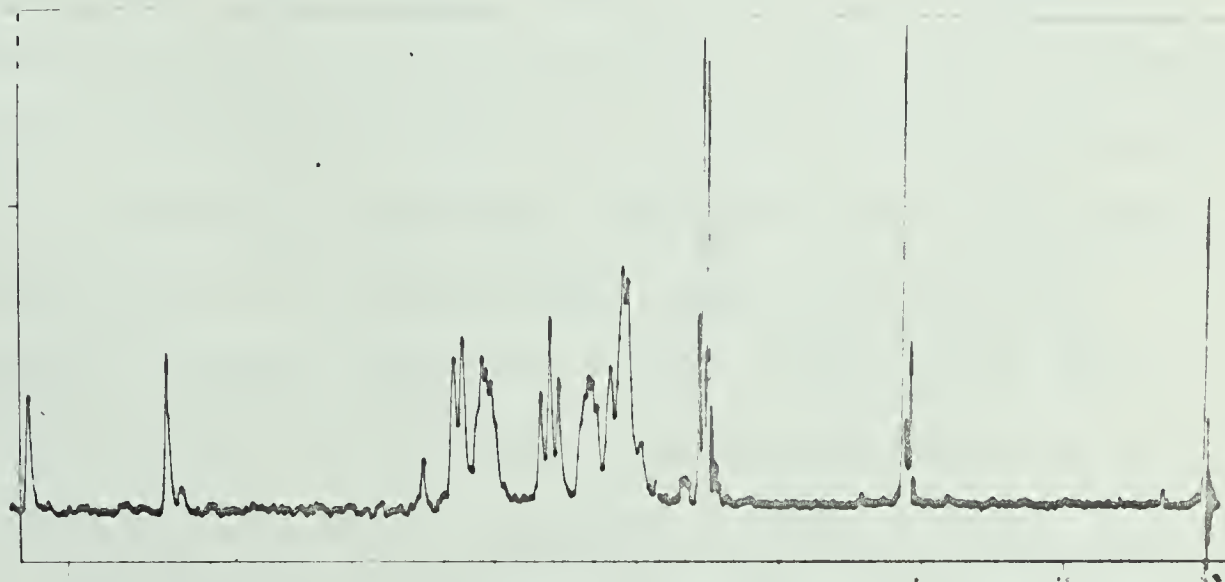


FIG. 39. P.M.R. spectrum (60 Mc.p.s.) of a sample from the reaction of XVI with methanol. (Run 2c, reaction time 25.6 hr). (DISCUSSION, Section 4).

eventual epimerisation to XXVII, suggest a methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitropentopyranoside structure. It must be expected that $J_{2,3}$, $J_{3,4}$ and $J_{4,5a}$ would be in the order of 8-10 c.p.s. should XXVI possess the α -xylo configuration. Since the values for these coupling constants were 4.1, 4.1 and 2.2 c.p.s., respectively, it follows that XXVI cannot have this configuration. Examination of the reduction products of impure XXVI showed that XXVI did not have the xylo configuration. In view of the isolation of the β -xylo diastereoisomer (XXVII), this configuration can also be eliminated. The configuration at the 3-position was readily shown through the reaction of XXVI with ethanol in the presence of triethylamine. The P.M.R. spectrum of the reaction product (Fig. 18) showed the presence of two types of ethoxy groups that together had an intensity for the C-methyl group about two-thirds of the sharp acetyl signal. The relative amounts of these two ethoxy groups was about 5:1. The triplet signal of the minor components centered at τ 8.9 has the same chemical shift as that observed for methyl 4-O-acetyl-2-deoxy-3-O-ethyl-2-nitro- β -D-xyloside (XXVIII). Since the substance responsible for this signal makes up about 10% of the product, and since the pre-epimerisation sample contained 9 mole % XXIV which was previously shown to give XXVIII with ethanol and triethylamine, this minor component is most probably the compound XXVIII. Two signals for methoxy groups were observed at τ 6.50 and 6.54 with relative intensities of about 1:3, respectively. This observation precludes the

presence of any appreciable amount of di-O-ethyl compound and requires that the major ethoxy group signal centered at τ 8.78) arise from a mono-O-ethyl-mono-O-methyl compound and that this compound comprise about half of the reaction mixture. It would then follow that about a third of the mixture consists of di-O-methyl compound(s). Examination of the signals in the τ 4.8 to 7.0 region clearly establish the presence of an about 2:1 mixture of the ethyl and methyl glycosides, respectively, of 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-xylosides containing approximately 10% of the above mentioned compound, probably XXVIII. This conclusion is drawn from the fact that the signals for H_2 , H_3 , H_4 and the two H_5 's, to the extent observable, correspond exactly both in chemical shift and coupling constants with those for the pure crystalline methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-xyloside (XXVII). The only difference is the chemical shift of H_1 for the corresponding ethyl glycoside XXIX. This signal, in view of the intensity required, is the doublet centered at τ 5.20 rather than that centered at τ 5.28 for XXVII. Although the relative intensities of these two signals could not be measured with accuracy, it is evident that these are about 2:1, respectively, as required by the other features of the spectrum mentioned above. A similar conclusion is reached when the integration for the region τ 4.8-7.0 is examined and the contribution by ethyl- CH_2 - signals taken into account.

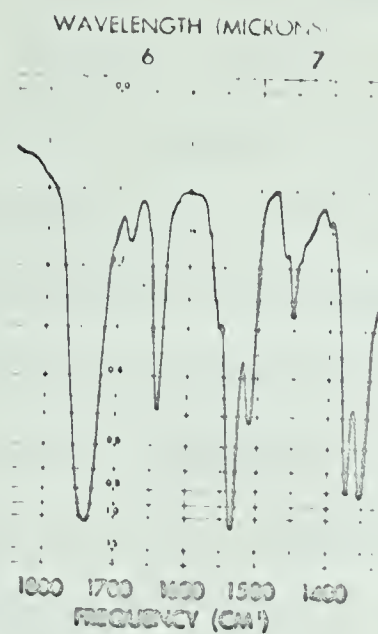
The formation of XXVII from XXVI through the agency of ethanol and triethylamine is most simply explained by

formation of the aci-salt from XXVI followed by its protonation to give XXVII. In all probability, had the acid salt eliminated methoxide ion in ethanol to form XXV, only ethyl glycoside would result. It therefore follows that the configurations at the 1- and 3- positions are the same as in XXVII and that XXVI is the 2-epimer of XXVII, namely, methyl 4-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-lyxoside. The formation of XXIX from XXVI in a yield of approximately 50% (after allowing for the XXV present in the starting mixture) shows that indeed the intermediate aci-salt was prone to elimination to form XXV. This assignment of configuration to XXVI was found to be in best agreement with the P.M.R. parameters which may be expected for the α -lyxo and β -lyxo configurations (see below).

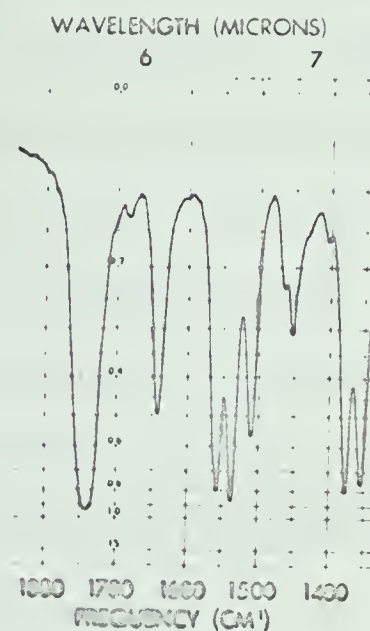
As described in the Experimental, the compositions of the samples isolated from the reaction mixture were assessed on the basis of integration of the 60 Mc.p.s. P.M.R. spectra. Qualitative confirmation of these analyses were given by the I.R. spectra (see p. 64, 140) several of which are reproduced, in part, in Fig. 40.

It was found that the rates of these processes were not always reproducible. Thus Runs 1 and 2 gave exactly

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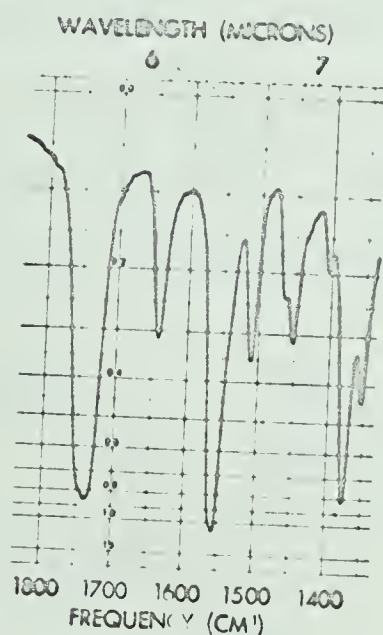


a

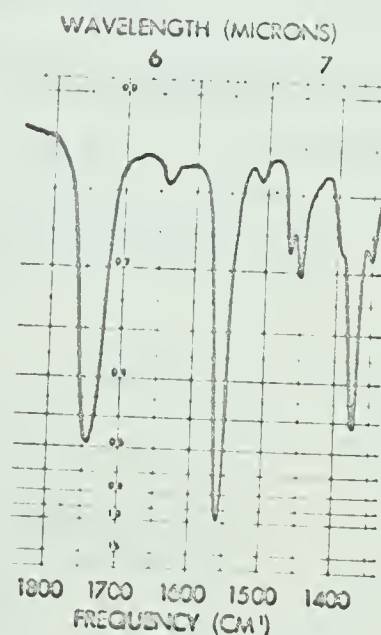


b

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c

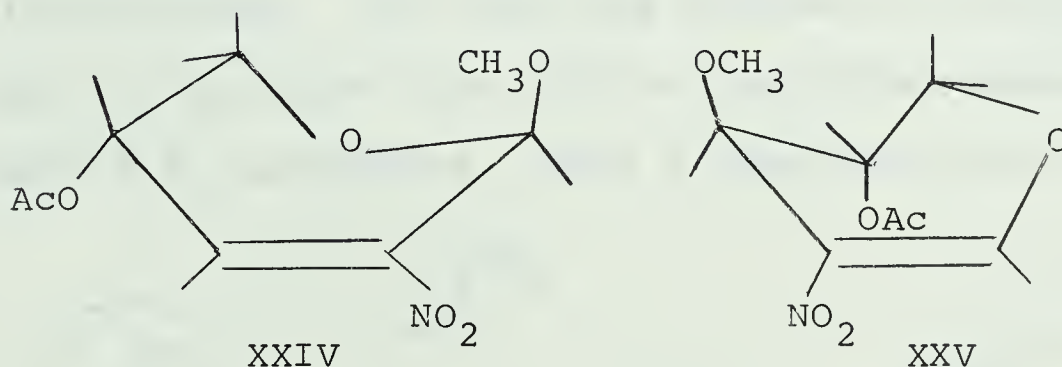


d

FIG. 40. I.R. spectra ($1350\text{--}1850\text{ cm}^{-1}$) of samples from the reaction of XVI with methanol. Reaction times (hr): a) 1.90; b) 8.60; c) 25.6; d) 70.7. Note especially the changes in intensity of the absorptions for the nitro group at $1509\text{--}1511\text{ cm}^{-1}$ [starting material (XVI) and the second intermediate (XXV)], 1538 cm^{-1} [The first intermediate (XXIV)], and $1560\text{--}1563\text{ cm}^{-1}$ [the saturated nitrocompounds (XXVI and XXVII)].

the same results, but Runs 3, 5, 6, 7 and 8 all gave a separate set of results. The chief difference between these results appeared to be the rate of reaction of the nitroglycal XXV with methanol, so that the maximum concentrations of this substance in the samples were 30 or 70 mole %, respectively, in the two sets of runs.

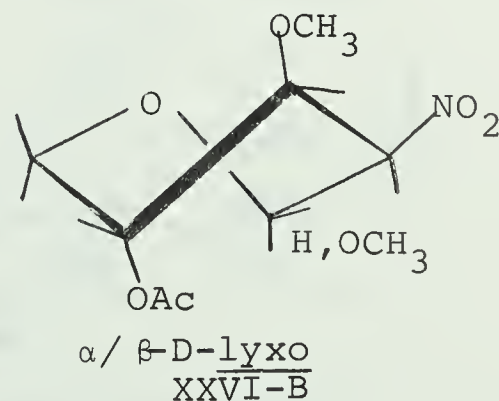
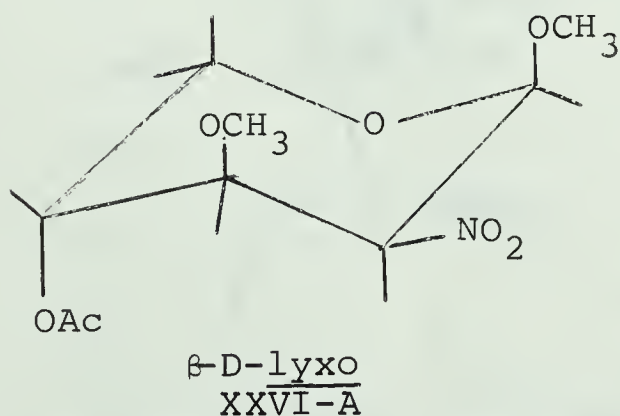
Before examining the mechanisms of this sequence of reactions, it is important to determine the conformations of the compounds XXIV to XXVII. Examination of the coupling interactions between the protons at the 4- and 5-positions (Table XIV) shows that compounds XVI, XXIV, XXV and XXVI all have small values for the $J_{4,5}$ coupling constants, and thus have the q-lH or lC conformations. By reason of the $A^{(1,2)}$ and anomeric effects (DISCUSSION, Section 1) XXIV should have the β -configuration and XXV



should have the xylo configuration. Since the ring structure contains no anchoring group to strongly favor either of the q-lH or q-Hl conformations, the alternative structures to those assigned would, in all probability, adopt the q-Hl conformation. The assignments are supported by lack of strong long-range allylic coupling ($J_{1,3}$) in either case, which is indicative of pseudo-axial allylic methoxy substituents

in XXIV and XXV. It is of interest to note that the large long-range $J_{3,5}$ coupling is with the H_5 at high-field. The planar "W" system is obviously formed much better with the proton that is disposed equatorially at the 5-position than that which is axial. The assignments of the observed signals, which were made on the general grounds that the signal to high-field is the axial proton (135), is thus questionable. The possible discrepancy may well be due to the diamagnetic anisotropy of the 2,3 double bond.

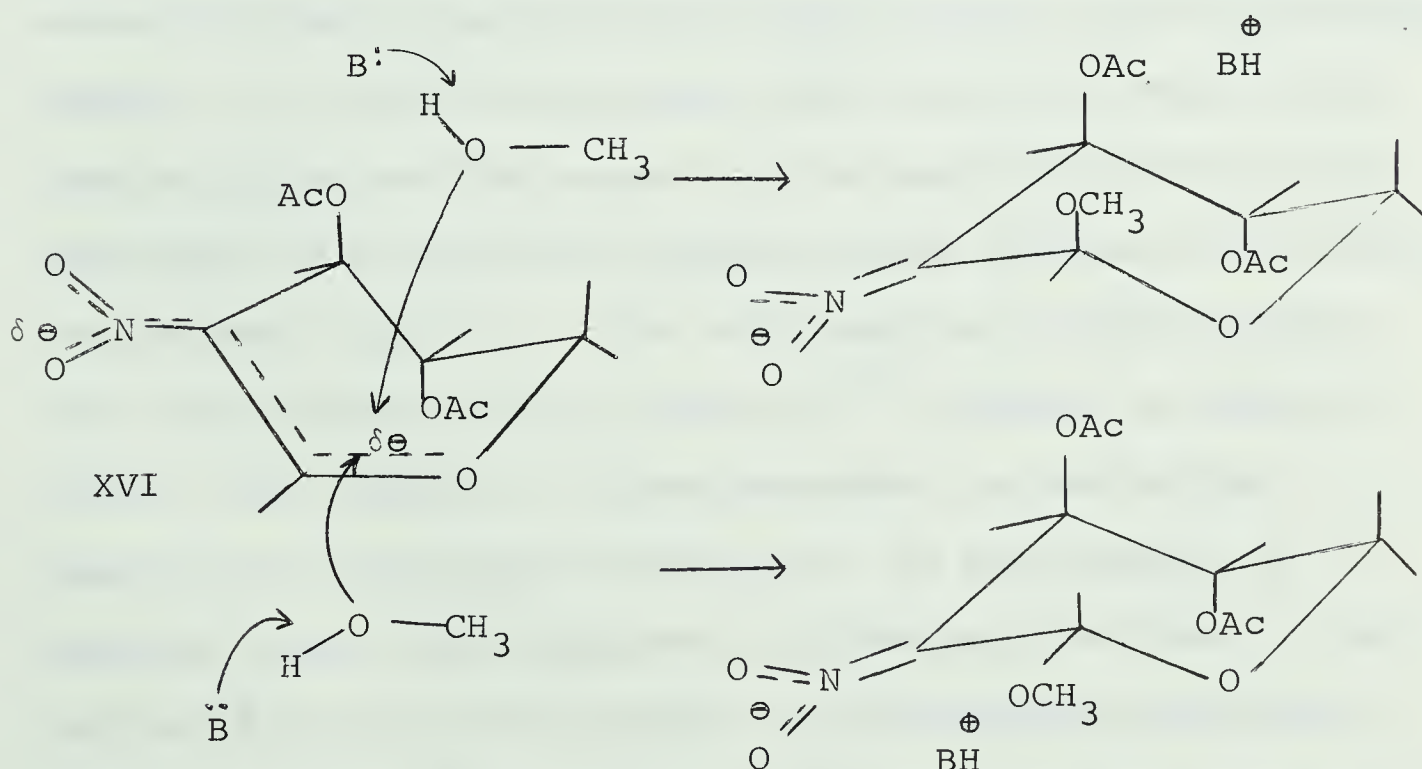
Other than the possible 1C conformation for XXVI, various skew-boat conformations must also be considered. Hendrickson (66) has calculated that the most stable flexible forms, i.e. skew-boats, have dihedral angles around the ring of 33° and 71° , and Coxon (137) has tabulated the six possible skew-boat forms for penta-O-acetyl- α -D-altropyranose. This data was adapted to the present system and only one skew-boat, XXVI-B, could be accommodated by the P.M.R. parameters. Such a skew-boat with the observed



coupling interactions could have either the α or β -D-lyxo configuration. However, these skew-boat forms are highly improbable since they have only been found (138) where tert-

butyl substituents or fused rings strongly constrain the ring. Thus, Coxon (137) found no evidence to suggest that penta-O-acetyl- α -D-altropyranose was in other than a C1 conformation. It can be seen that with either α or β -D-lyxo configurations, skew-boat XXVI-B is not highly favored since strong diaxial and gauche interactions are present in these two configurations, respectively. In the 1C conformation (XXVI-A) only the β anomer of the two lyxo configurations can have a $J_{1,2}$ value less than 7-10 c.p.s.

The attack by methanol on 3,4-di-O-acetyl-2-nitro-D-xylal (XVI) is highly stereospecific and demonstrates that one reaction route must be generally favored over the other.



A kinetic study (see below) showed the first reaction to be strongly base-catalysed and weakly acid-retarded. Since nucleophilic attack on glycals has usually been strongly acid-catalysed by protonation of the leaving group at the 3-

position, some property of the nitro function must completely alter the reaction mechanism. Addition to nitroolefins has been regarded (139) as proceeding by way of the aci-nitro form and this species is taken to be the transition state here. Consideration of the two aci-nitro transition states reveals that α attack involves a strong $A^{(1,3)}$ interaction, and this is regarded as the source of the stereospecificity of the reaction. The $A^{(1,2)}$ and $A^{(1,3)}$ effects (60, 140) are of sufficient magnitude that, where applicable, usually only one of the two possible products can be detected.

The presence of the good leaving group at the 3-position in XVI made it highly probable that this would eventually be protonated and removed from the molecule. However, the reaction product, XXIV, does not have a good leaving group and the course of its reaction with methanol was found to be entirely dependent upon whether or not base was present (Fig. 41). The conformation of XXIV is such that the favored path of attack ($A^{1,3}$ effect) by methanol places this reagent in close proximity to the methoxy function at the anomeric position. In the absence of external base, this function is protonated and lost. The driving force for the reaction is probably the reduction in ground-state energy achieved by increased conjugation of the nitroolefinic system. The magnitude of the shift in frequency of the nitro asymmetric stretching absorption (Table XV) shows this to be a relatively large effect, it

having been shown that this absorption is sensitive to conjugation (126,141).

Direct observation in a P.M.R. spectrometer of the reaction of XVI with methanol showed the subsequent reaction of XXIV with methanol to be essentially complete after half an hour in the presence of 1.0 mole-equivalent of triethylamine and 6.6 mole-equivalents of methanol.

This reaction of XXIV with methanol gave the β -xylo compound XXVII as the only observable product, i.e. compounds XXV and XXVI were not involved as intermediates to any appreciable extent. Examination of Table XVI shows that, by comparison, the uncatalysed reaction of XXIV with methanol is essentially complete only after a period of days or weeks. When the sample isolated from Run 2b (65 mole % XXIV) was subjected to the original reaction conditions but without the acetic acid produced in the production of XXIV, the reaction path was not affected to any appreciable extent. Thus, the conversion of XXIV to XXV in the uncatalysed reaction is not dependent upon this small concentration of acetic acid for protonation of the aglycone. The effect of triethylamine is considered to involve normal base catalysis with preferred protonation of this external base. This resultant conjugate acid of triethylamine is then able to move and to protonate the most suitable site. This would be at a position as close as possible to the site of the negative charge since we must expect the dipolar attraction

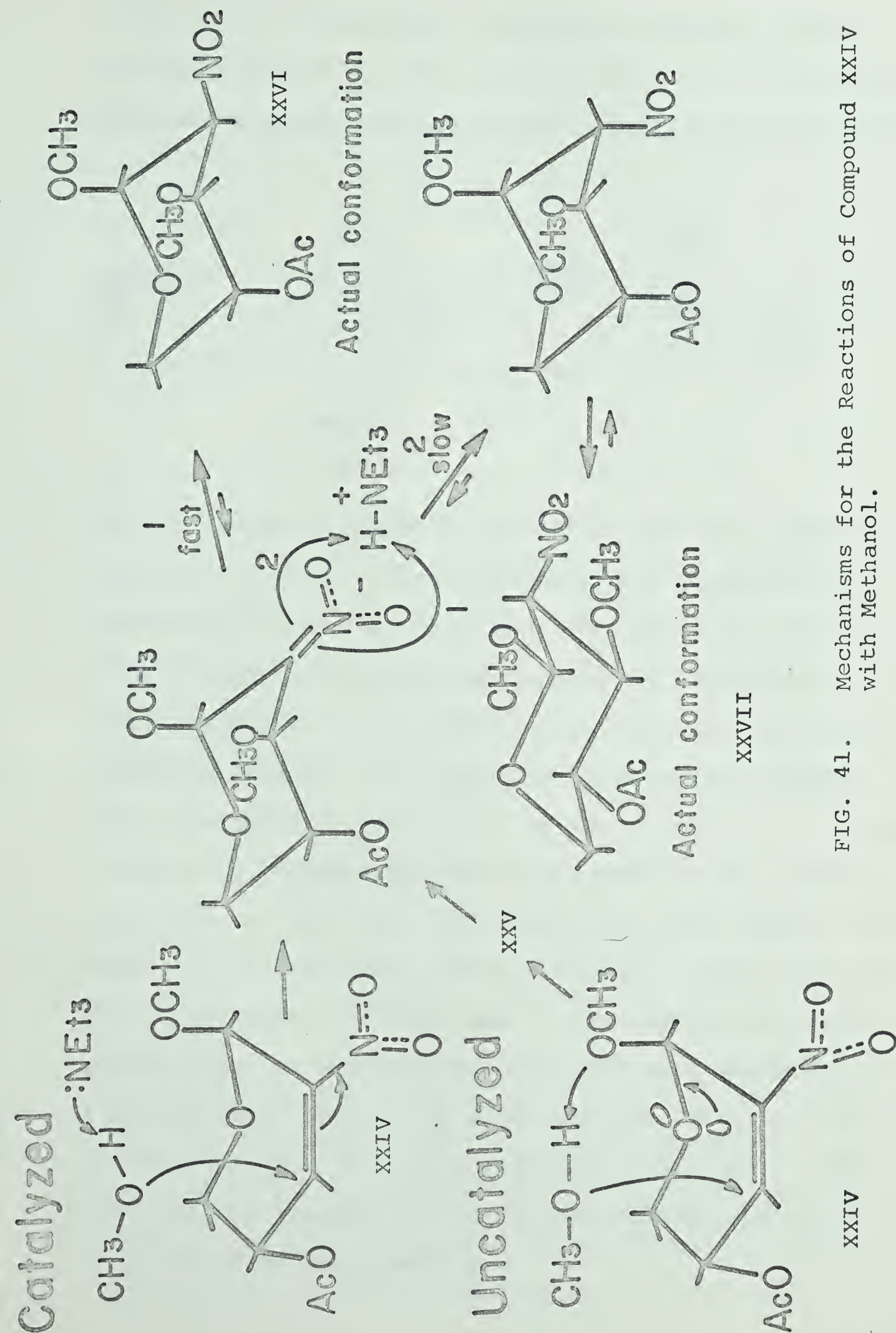
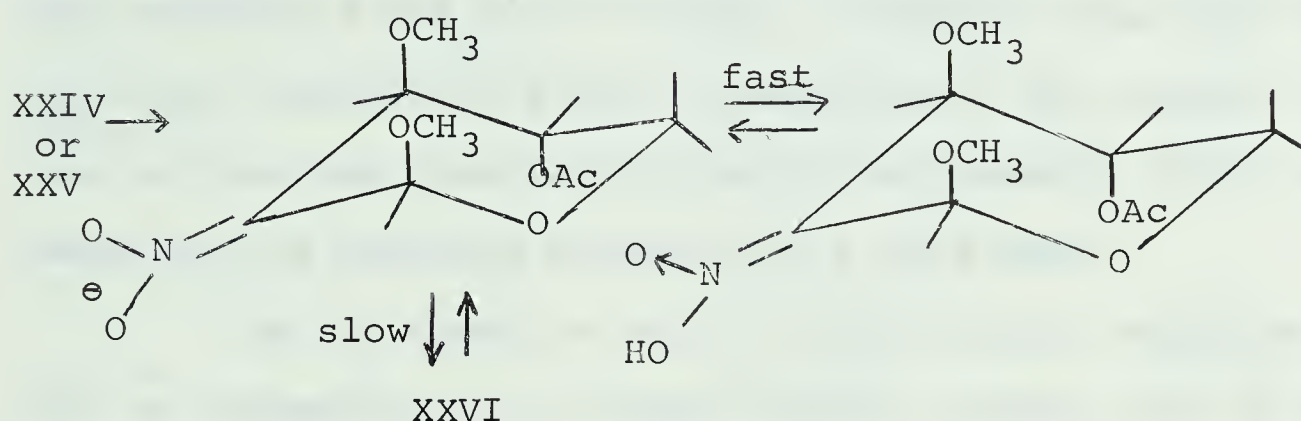


FIG. 41. Mechanisms for the Reactions of Compound XXIV with Methanol.

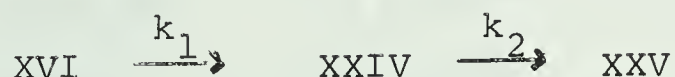
to decrease the distance of charge-separation. Since aci-nitro compounds have been isolated (82), the sterically-unhindered aci-nitro oxygens are probably protonated first.



However, such a product is unstable (82) and must be expected to yield a corresponding nitro compound by protonation at the 2-position. For reasons of the $A^{1,3}$ effect, this latter protonation must be expected to take place trans to the more sterically hindering substituents as has been shown for 1-aci-nitro-2-phenylcyclohexane (60,82). Thus, the initial protonation at the 2-position is expected to give the β -lyxo configuration since the two methoxy functions at the 1 and 3-positions are much closer to the reaction site than the acetyl function at the 4-position. In the presence of strong base, this kinetically controlled product must be expected to yield the more thermodynamically stable product (XXVII) by epimerisation (Fig. 41) which is a facile process for nitro compounds (82, 142). Thus XXVI was not observed in the triethylamine-catalysed reaction of XVI with methanol.

As indicated in Fig. 41, the same aci-nitro transition state must be arrived at from compound XXV, because by analogy with the reaction of XVI, compound XXV must be attacked by methanol cis to the 3-methoxy function for reasons of the $A^{(1,3)}$ effect. However, when this same aci-nitro transition state is protonated, the absence of base allows the kinetically-controlled product (XXVI) to exist in the reaction mixture for a long time.

As was shown in Fig. 36, the initial reaction of XVI is accompanied by a large rotation change, and so this reaction was studied polarimetrically. This reaction was previously found to be stereospecific and considerably faster than the reaction of the product, XXIV, with methanol. The initial polarimetric rates were used to avoid errors inherent in neglecting the latter factor and the rapid increase in concentration of acetic acid.



$$k_1 > k_2$$

The values for the velocity constant (k_1) for the reactions of compound XVI were readily calculated from the initial polarimetric rates (EXPERIMENTAL, Section 4.(b)) after the rotation of pure XXIV had been determined and the reaction of XVI with methanol shown to be first-order in

TABLE XVII

The Influence of Solvent and Alcohol upon the Value of the
Velocity Constant (k_1) - Uncatalysed Reactions ^a

<u>Solvent</u> ^b (v/v)	<u>Alcohol</u>	k_1 ^d (liter mole ⁻¹ sec ⁻¹)	<u>Relative Rate</u>
DMSO ^c	CH ₃ OH	2.7×10^{-5}	2.30
Methanol	"	1.5×10^{-5}	1.31
50% DMSO ^c , 50% benzene	"	1.5×10^{-5}	1.27
Benzene	"	1.2×10^{-5}	1.00
Benzene + 0.74M CCl ₃ COOH	"	8.1×10^{-6}	0.7
DMF ^c	"	7.1×10^{-6}	0.60
33% THF ^c , 67% benzene	"	1.7×10^{-6}	0.14
1,4-dioxan	"	1.0×10^{-6}	0.09
THF ^c	"	6.4×10^{-7}	0.05
Benzene	CH ₃ CH ₂ OH	5.4×10^{-6}	0.46
Benzene	ϕ CH ₂ OH	4.4×10^{-6}	0.38

a. [Alcohol] = 4.98M, [XVI] = 0.082M, T = 26°.

b. Solvent; 20% methanol and ~78% stated solvent, (v/v).
Concentrations of CH₃CH₂OH and ϕ CH₂OH proportionally higher.

c. DMSO = dimethylsulfoxide, DMF = N,N-dimethylformamide,
THF = tetrahydrofuran.

d. Calculated from initial reaction rates.

methanol (Table V). Solvent effects upon the initial rotations were taken into account when making these calculations and, in any case, did not change the initial rotation of the reaction mixture to any large extent. The strong solvent effects upon the reaction rates are seen by examination of Table XVII.

The solvent effects do not follow the order of solvent polarity but, when the basic solvents N,N-dimethylformamide, 1,4-dioxan and tetrahydrofuran are omitted, the k_1 order becomes dimethylsulfoxide > methanol > (50% dimethylsulfoxide-50% benzene) > benzene. The variation in k_1 is only by a factor of 2.3 between the extremes of this new series. Such an order and k_1 variation is not incompatible with solvent effects upon a reaction involving ionic transition states. Since the reaction between XVI and alcohols is strongly base-catalysed (Table XVIII), it might have been expected that basic solvents would increase the reaction rate.

Since basic solvents retard the reaction rate, any possible rate enhancement must be obscured by another, more powerful, effect. As the reaction involves an attack at an electrophilic site, it is considered that strong solvation by basic solvents hinders the approach of the nucleophile and/or lowers the ground state energy of XVI. The postulated aci-nitro transition state would not be similarly solvated by basic solvents and thus would increase the net activation energy of the reaction. This hypothesis is supported by the decrease in observed velocity constants when using

TABLE XVIII

The Catalysed Reaction of XVI with Methanol ^a

$\frac{[\text{Acid/base}]}{(\text{mole liter}^{-1})}$	pK_a ^b	$\frac{K_1}{(\text{liter mole}^{-1} \text{sec}^{-1})}$	$\frac{\text{Relative Rate}}{\text{Rate}}$
0.25 triethylamine	10.7	8.80×10^{-4}	103.8
0.25 2,4,6-collidine	7.5	5.6×10^{-5}	6.6
0.25 2,6-lutidine	6.6	3.0×10^{-5}	3.6
0.25 2-picoline	6.0	3.4×10^{-5}	4.0
0.25 pyridine	5.2	3.7×10^{-5}	4.5
None	-	8.5×10^{-6}	1.0
4.4 acetic acid	-6.1	4.2×10^{-6}	0.5

^a. [XVI] = 0.05M, [CH₃OH] = 1.25M, T = 26°.^b. From ref.143. (Values for aqueous solutions).

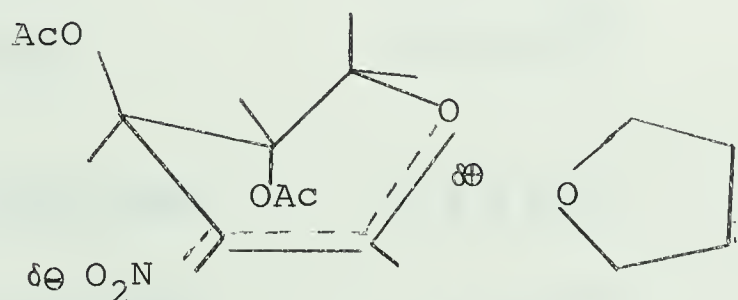
as the cosolvent benzene 1,4-dioxan or tetrahydrofuran solvents with increasing basicities but similar dielectric strengths.

The catalytic effect of bases on the reaction of XVI with methanol is shown to be enhanced by increased base strength and by decreased steric hindrance (Table XVIII). The retarding effect of acids is also shown. In the case where trichloroacetic acid was used, the reaction mixture was examined by P.M.R. spectroscopy when its observed

rotation became positive. There were no signals present that suggested that anything other than the usual uncatalysed reaction of XVI with methanol had occurred (cf. Fig. 41).

The reaction of XVI with other alcohols could be conveniently studied in the presence of base and the results are presented in Table XIX. The results show that the alcohol structure is important both in the expected steric effects and in the variation in the acidity of the alcohol. The results also show that the retarding effect of tetrahydrofuran is still operative even in the presence of strong base catalysis.

Compound XVI is envisaged as having some dipolar character and, as previously mentioned, it is believed that solvation of the partial oxocarbenium portion of the molecule reduces its ground-state energy. The rates of reaction



XVI with methyl, ethyl and isopropyl alcohols (Table XIX) are in the order expected for reasons of steric hindrance. However benzyl and benzhydryl alcohols react faster than ethyl and isopropyl alcohols, respectively, which indicates that the acidity of the alcohol can be at least as important as the steric hindrance effects. When the rates of reaction of XVI with methyl, ethyl and benzyl

TABLE XIX

The Catalysed Reaction of XVI with Alcohols.^a

<u>Solvent</u> ^b	<u>Alcohol</u> ^c	k_1 (liter mole ⁻¹ sec ⁻¹)	Relative Rate
Benzene	p-O ₂ NφCH ₂ OH	1.5 x 10 ⁻⁴	1.59
"	p-CH ₃ OφCH ₂ OH	1.2 x 10 ⁻⁴	1.24
"	ClCH ₂ CH ₂ OH	1.1 x 10 ⁻⁴	1.14
"	CH ₃ OH	9.3 x 10 ⁻⁵	1.00
"	φCH ₂ OH	9.1 x 10 ⁻⁵	0.98
"	CH ₃ CH ₂ OH	3.4 x 10 ⁻⁵	0.36
"	φ ₂ CHOH	4.7 x 10 ⁻⁶	0.050
"	(CH ₃) ₂ CHOH	3.5 x 10 ⁻⁶	0.038
Benzene ^d	CH ₃ OH	8.0 x 10 ⁻⁴	1.00
63% THF ^d , 37% benzene	CH ₃ OH	1.9 x 10 ⁻⁴	0.24
Benzene ^d	(CH ₃) ₂ CHOH	1.3 x 10 ⁻⁵	1.0
85% THF ^d , 15% benzene	(CH ₃) ₂ CHOH	8 x 10 ⁻⁶	0.6

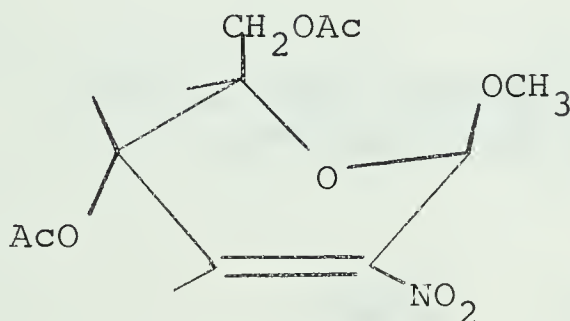
^a. [XVI] = 0.050M, temperature 26°.^b. [2,4,6-collidine] = 0.760M, except as noted.^c. [Alcohol] = 1.25M.^d. [Triethylamine] = 0.150M.

alcohols are examined, it is seen that the more acidic alcohols undergo greater acid catalysis (Tables XVII and XIX). Since nitro groups have been found to form weak hydrogen-bonds (144), it may well be that the more acidic alcohols retard their own uncatalysed reactions with XVI by hydrogen-bonding with XVI rather than reacting at the 1-position. p-Methoxybenzyl and p-nitrobenzyl alcohols were reacted with XVI in an attempt to find a clear correlation with some factor such as the Hammett σ function (145), but as shown in Table XIX, both of these alcohols react considerably faster than unsubstituted benzyl alcohol. It is possible that the p-methoxy function has a special affinity for XVI as does tetrahydrofuran etc., and that this allows for a rate enhancement which is not elucidated at this time.

5. The Reaction of 3,4,6-Tri-O-acetyl-2-nitro-D-glucal (XIII) with Methanol.

It was shown previously (DISCUSSION, Section 4) how 3,4-di-O-acetyl-2-nitro-D-xylal (XVI) reacted with methanol and with methanol and triethylamine. The two main features of the results were (a) the remarkable stereospecificity of every reaction, and (b) the change in reaction course in the presence of moderate amounts of triethylamine although the same compound was obtained as final product. Compound XIII has the same stereochemistry as XVI, although it was considered that the acetoxymethylene function at the 5-position could

Gluco
analogue
of XXIV



have an "anchoring" effect on certain conformations, e.g. a gluco analogue of XXIV would have this function axially disposed. This would tend to counteract the effects which led specifically to a β -configuration for XXIV. Besides an uncatalysed run, several base-catalysed runs were performed to ascertain the effect of base on the reaction course.

Compound XIII was found to react with methanol in a fashion analogous to that of XVI. However, certain differences were immediately evident. In the uncatalysed reaction, the first isolable material had I.R. and P.M.R. spectral characteristics (Tables XX and XXI) very similar to

TABLE XX

Infra-red Absorptions (cm^{-1}) of Compounds
Involved in the Reaction of XIII with Methanol

	XIII	XXX XXXI	XIV XXXII	XXXIII XXXIV XXXV
Nitro assymetric stretch	1510s	1538s	1513s	\sim 1565s
Alkene C=C stretch	1645s	\sim 1685w	1642s	-
Acetoxy C=O stretch	Strong, broad absorption, 1730 - 1760 cm^{-1} , for all.			
Methoxy C-H stretch	-	\sim 2845w	\sim 2845w	\sim 2845w

w, m, s indicate weak, medium or strong absorptions.

those of XXIV, but was a mixture of two compounds with singlets at τ 4.45 and 4.55. These were assigned to compounds XXX and XXXI, respectively. As the reaction proceeded, two new singlets of low intensity appeared at τ 1.80 and 1.84.

Later the P.M.R. and I.R. spectra showed saturated products to be present. After correlation of the reaction mixture rotations with the sample compositions (Table XXII),

TABLE XXI

The P.M.R. Parameters of Compounds Involved in the
Reaction of XIII with Methanol

Compound	Chemical Shifts (τ)				Coupling Constants (c.p.s.)				
	H ₁	H ₂	H ₃	H ₄	J _{1,2}	J _{2,3}	J _{3,4}	J _{4,5}	J _{1,3}
XIII <u>a</u> <u>b</u>	1.67	-	4.01	4.73	-	-	2.9 ^f	2.0	0.3
XXX <u>c</u>	4.45	-	2.83	4.85	-	-	4.5 ^f	1.2 ^f	0.4 ^f
XXXI <u>c</u>	4.55	-	2.82	4.47	-	-	2.4 ^f	?	0.5
XIV <u>a</u> <u>b</u>	1.80	-	5.62	4.70	-	-	2.7 ^f	1.5 ^f	0.3
XXXII	1.84	-	?	?	-	-	?	?	0.5
XXXIII <u>a</u> <u>d</u> (β - <u>gluco</u>)	5.24	5.51	5.93	4.97	8.1	10.1 ^f	9.6	10.0 ^f	0
XXXIV <u>d</u> <u>e</u> (α - <u>gluco</u>)	4.81	5.46	5.73	4.98	4.0	10.2 ^f	9.0 ^f	10.3 ^f	0
XXXV	4.5 and up.								

a. Determined on a 20% w/v CDCl₃ solution of pure compound at 100 Mc.p.s.

b. The complete spectrum is given in Table X (DISCUSSION, section 1).

c. Present in a mixture examined as a 20% w/v CDCl₃ solution at 100 Mc.p.s.

d. Complete spectrum presented in EXPERIMENTAL, section 7.

e. Impure 10% w/v CDCl₃ solution at 100 Mc.p.s.

f. Demonstrated by double irradiation.

TABLE XXII

The Compositions of Samples Isolated from the Reaction of
XIII with Methanol ^a

Run	Reaction Time (hr)	Observed Rotation (deg.) ^b	Composition (mole %)					Saturated Products ^c
			XIII	XXX + XXXI	[XXX] [XXXI]	XIV + XXXII	[XIV] [XXXII]	
1a	1.1	+0.54	60	40	~50/50	0	-	0
1b	2.3	+0.88	44	50	~50/50	6	~65/35	trace
1c	3.7	+1.18						
1d	6.1	+1.52	6	57	~40/60	25	~75/25	~12
1e	9.2	+1.74	~3	51	~35/65	24	~75/25	22
1f	12.0	+1.87	0	46	~20/80	34	~80/70	20
1g	22.1	+2.04	0	35	d	32	~75/25	32
1h	34.3	+2.07	0	33	d	30	~75/25	37
1i	78.1	+2.00	0	28	d	16	~75/25	56
1j	167	+1.75	0	17	d	~10	d	~73
1k	263	+1.59	0	trace	d	trace	d	100
1l	360	+1.42	0	0	-	0	-	100
1m	538	+1.34	0	0	-	0	-	100
1n	800	+1.12	0	0	-	0	-	100
1o	1030	+1.10	0	0	-	0	-	100

a. The concentration of XIII was initially 0.0648 M in a 75% methanol-25% benzene (v/v) solution.

b. Observed rotation for a 10 cm polarimeter tube.

c. The relative concentrations of saturated products did not appreciably change throughout the reaction from time 167 to 1030 hours. Compounds XXXIV and XXV were major products, XXXIII a minor product.

d. The P.M.R. was too indistinct for complete analysis.

it was calculated that the initial reaction rate was approximately one-third of that for the reaction of XVI with methanol.

The compositions of the samples were determined by examination of their P.M.R. spectra. The lack of stereospecificity in the first reaction greatly complicated the spectra (an example of which is shown in Fig. 42) and led to less accurate results. In particular, the mixture of saturated products gave numerous signals which made difficult even qualitative estimations of the reaction product composition. However, in the early stages of the reaction sequence, some useful information could be obtained. The two first-formed compounds, XXX and XXXI, were assigned the β and α -anomeric configurations since, as mentioned previously in section 1 of this Discussion, it has been generally found that in P.M.R. spectroscopy of these systems the β -anomeric signal is at lower-field than that of the α -anomeric proton. As the reaction proceeded, the ratio of concentrations of XXXI to XXX increased, and enabled a limited examination of XXXI to be made. Several base-catalysed reactions were also examined by stopping the reaction after suitable periods of reaction time and the results are presented in Tables XXIII and XXIV. In Run 3a (4.5 hr reaction time), the concentration of compound XXX was sufficiently high that several of its coupling interactions could be discerned (Table XXI). These indicated compound XXX to be the β -anomer and therefore XXXI to be the α -anomer of the 2,3-unsaturated intermediates.

TABLE XXIII

The Compositions of Samples Isolated from the Triethylamine-catalysed

Reaction of XIII with Methanol^a

Run	<u>Reaction Time</u> (hr)	<u>Observed Rotation</u> (deg) ^b	Composition (mole %).				
			XIII	XXX +	[XXX] [XXXI]	XIV +	Saturated
				XXXI			XXXII
With 1.00 Mole-equivalent Triethylamine							
2a	0.27	+1.05	24	69	~50/50	d	5
2b ^c	0.72	+1.23	≤2	78	~45/55	d	22
2c ^c	1.7	+1.04	0	44	~40/60	d	56
2d	3.9	+0.73	0	≤13	-	0	≥87
2e	9.0	+0.53	0	0	-	0	100
With 0.02 Mole-equivalent Triethylamine							
3a ^c	4.5	+0.91	~12	62	~60/40	~6	~20
3b	1.3	+0.66	0	16	-	~9	75
3c	20.6	+0.52	0	~9	-	~5	86
3d	37.4	+0.38	0	0	-	0	100
3e	330	++0.24	0	0	-	0	100

a. The concentration of XIII was initially 0.0648M in a 75% methanol-25% benzene (v/v) solution.

b. Observed rotation for a 10 cm polarimeter tube.

c. Also examined at 100 Mc.p.s. as a 10% w/v deuteriochloroform solution.

d. If present, the concentration of XXXIII is less than 2 mole %.

e. The major saturated product was XXXIII. Deacetylation of the samples from Runs 2d and 3b confirmed this finding.

TABLE XXIV

The Compositions of Samples from the Triethylamine-catalysed Reaction of XIII with Methanol ^a

Run	Reaction Time (hr)	Observed Rotation (deg.) ^b	Composition (mole %)				Products de-O-Ac. ^d
			XIII	XXX +	XXXI +	XIV +	
4a	0.08	+0.62	0	≤15	≤5	≥80	Only XXXIII
4b	0.37	+0.52	0	≤14	0	≥86	Only XXXIII
4c	2.5	+0.31	0	0	0	100	-
4d	9.3	+0.29	0	0	0	100	-
4e	22.5	+0.28	0	0	0	100	XXXIII 95 XXXIV 5
4f	300	+0.36	0	0	0	100	XXXIII 85 XXXIV 15

- ^a. The initial concentrations (M) in benzene were: XIII, 0.085; Et₃N, 0.192; CH₃OH, 3.3.
- ^b. Observed rotation for a 5 cm polarimeter tube.
- ^c. The initial saturated product was essentially only XXXIII; the concentration of XIII then slowly decreased.
- ^d. Contains the corresponding deacetylated derivatives of the stated compounds.

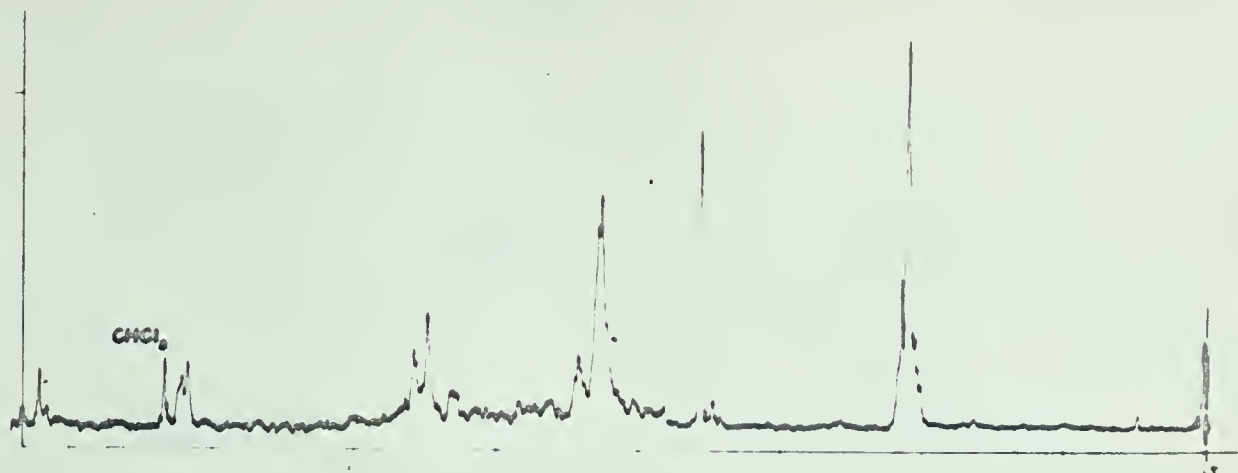


FIG. 42. P.M.R. spectrum (60 Mc.p.s.) of the sample from the reaction of XIII with methanol. (Run 1d, 6.1 hr). (DISCUSSION, Section 5).

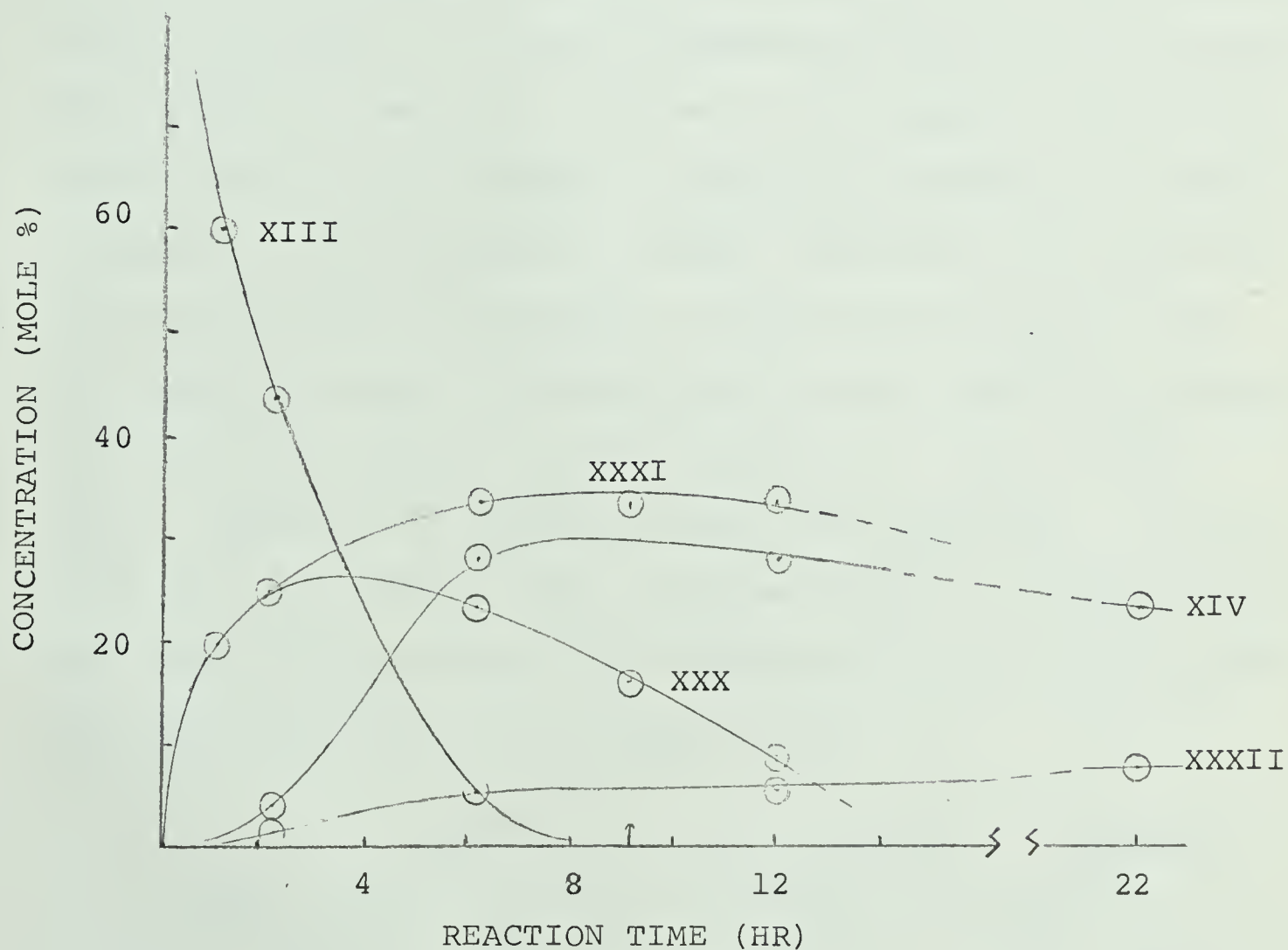
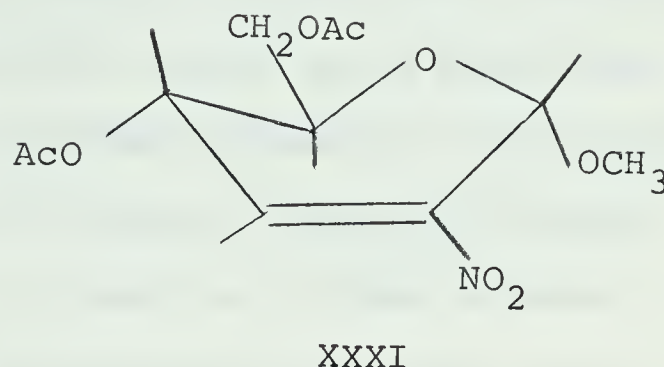
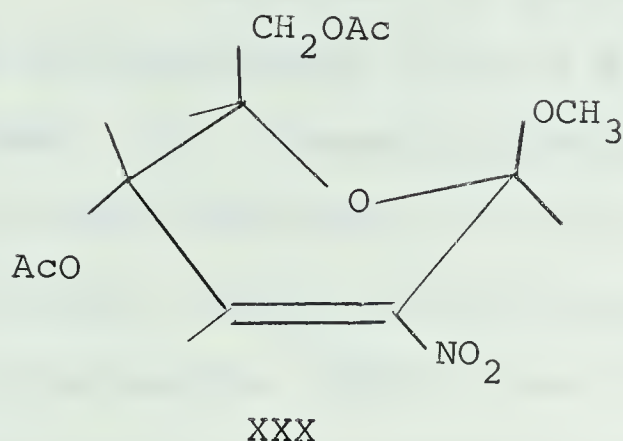
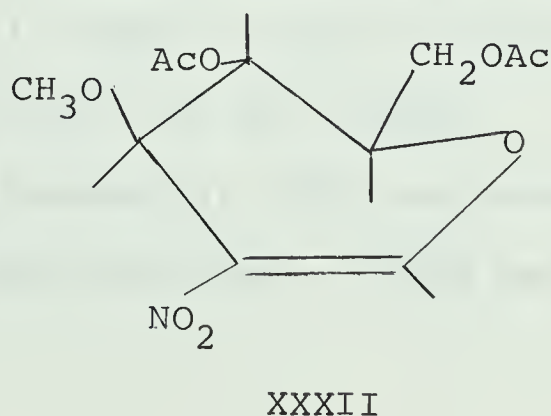
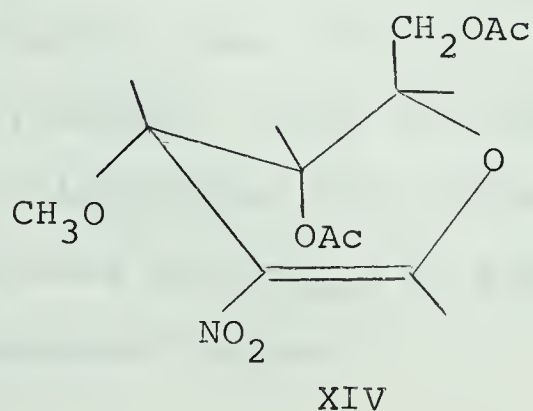


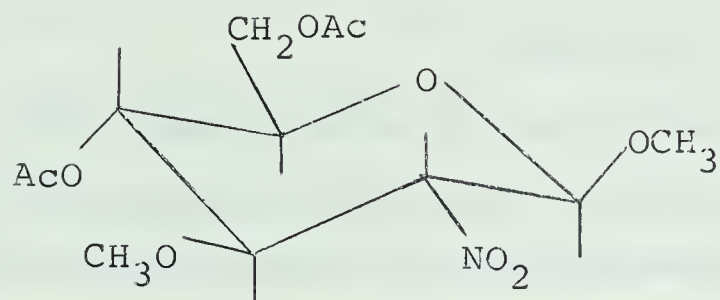
FIG. 43. Concentrations of olefinic compounds involved in the uncatalysed reaction of XIII with methanol. (DISCUSSION, Section 5, see Table XXII).



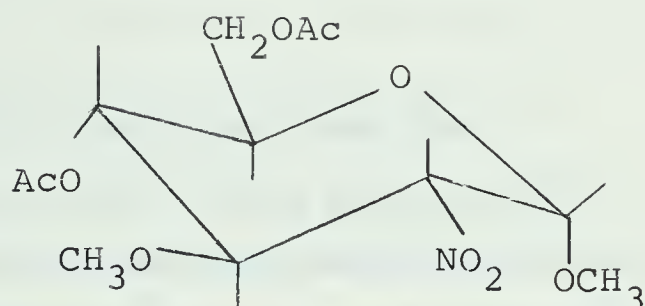
The two singlets of low intensity which appeared at τ 1.80 and τ 1.84 were assumed, by analogy with the formation of XXV from XVI, to be the corresponding D-glucal and D-allal derivatives. The P.M.R. spectra of the samples were not of sufficient clarity to permit immediate assignment of these compounds to the signals. However, admixture of a solution of 4,6-Di-O-acetyl-3-O-methyl-2-nitro-D-glucal (XIV) with the sample from Run 1d showed quite clearly that its presence increased the intensity of the signal at τ 1.80. Thus, if these compounds are indeed glycals, the signal at τ 1.80 is that of H_1 of compound XIV. This assignment is supported by the rates of appearance and disappearance (Fig. 43) of these two compounds which are discussed later.



The nature of the non-olefinic products is obscured by the complexity of the P.M.R. spectra in the region upfield from τ 4.5. Chromatography produced little or no separation of these substances. In the uncatalysed reaction, the analogue of XXVII, methyl 4,6-di-O-acetyl-2-deoxy-3-O-methyl-2-nitro- β -D-glucoside (XXXIII), was only formed as a minor product. No significant increase in the concentration of XXXIII was noted after a prolonged reaction time. The conformation and configuration of XXXIII were clearly evident from the P.M.R. spectrum (Fig. 19) which required the protons at the 1, 2, 3, 4 and 5 positions to all be axial. Furthermore, polarimetric monitoring of the reaction of XIV with methanol and triethylamine to yield XXXIII gave a straightforward rotation versus time curve indicative of the occurrence of one reaction. Therefore, the configuration of XXXIII is β -D-gluco. Low concentrations of methyl 4,6-di-O-acetyl-2-deoxy-3-O-methyl-2-nitro- α -D-glucoside (XXXIV) were noted, besides a high concentration of unidentified compound which was designated as species XXXV. The conformation of XXXIV was evident from the P.M.R. spectrum (Fig. 20). The rotations of XXIII and XXXIV. $[\alpha]_D^{25} -5^\circ$ and $[\alpha]_D^{26} +107^\circ$, respectively, show that Hudson's rules (146) are obeyed in these 2-deoxy-2-nitro-glycosides. Since the compound XXXII had the D-allo - configuration, the unidentified product(s) XXXV was considered to have the D-allo or D-altro configuration. XXXV was not examined further.



XXXIII



XXXIV

Deacetylation of several reaction mixtures in acidic conditions led to mixtures in which the signals of the anomeric protons were virtually the same as those of the acetylated compounds. However, the signals of protons at the 4-positions of these compounds were now outside the region of interest and allowed better analyses of the mixture of products. Chromatography failed to give any useful preparative separation of these deacetylated compounds although allowing confirmation of the trends found from examination of the P.M.R. spectra.

The triethylamine - catalysed reaction of XIII with methanol was closely examined as it was observed that the yield of compound XXXIII is highly dependent upon the presence of base. As is seen in Tables XXIII and XXIV, the formation of the nitroglycols XIV and XXXII is prevented by the presence of sufficient triethylamine. Since examination of Table XXV shows that the anomerisation of the saturated products is very slow, the observed anomeric configurations of the saturated products are determined by the initial attack upon XIII at high triethylamine concentrations. Inspection

TABLE XXV

The Compositions of the Products Isolated from the
Triethylamine-catalysed Reaction of XIII with Methanol ^a

<u>Run</u>	<u>Variable</u>	<u>Product</u> <u>b</u>	<u>Product</u> <u>c</u> <u>de-O-Ac</u>
0.088 M XIII and 0.20 M Triethylamine			
5	23.0 M Methanol		
6	16.6 "	↓	Average ~85%.
7	9.6 "	~90%	
8	16.6 "	↑	
0.088 M XIII and 16.6 M Methanol			
9	0.026 M Et ₃ N	≤20%	-
10	0.061		≤50%
11	0.089	↓	-
12	0.11		-
6	0.20	~80%	~80%
13	1.00	≤50%	~50%
16.6 M Methanol and 0.061 M Triethylamine			
10	0.080 M XIII	↓	<50%
14	0.020	~80%	~80% <u>d</u>
15	0.0061	↑	~75% <u>d</u>

^a. Method of mixing; the benzene solution was treated with methanol, then immediately with triethylamine, except in run 8, where triethylamine was added 10 min prior to methanol addition.

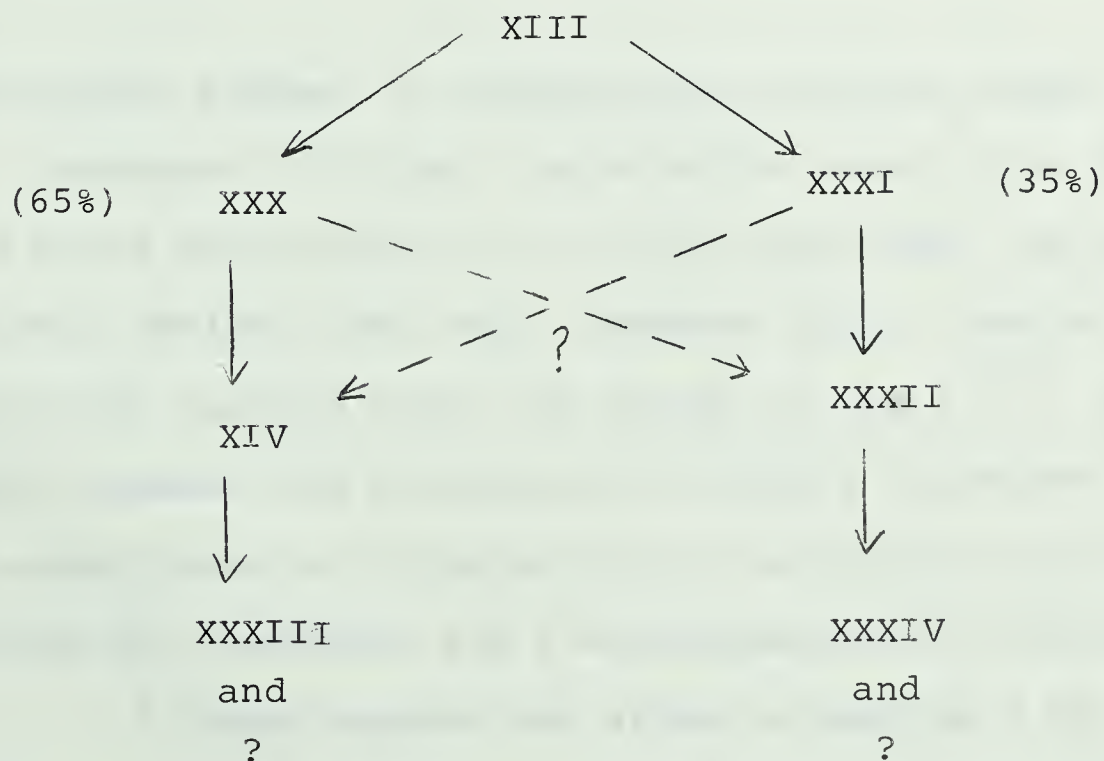
^b. Expressed as increasing concentration of XXXIII.

^c. Expressed as concentration of deacetylated XXXIII.

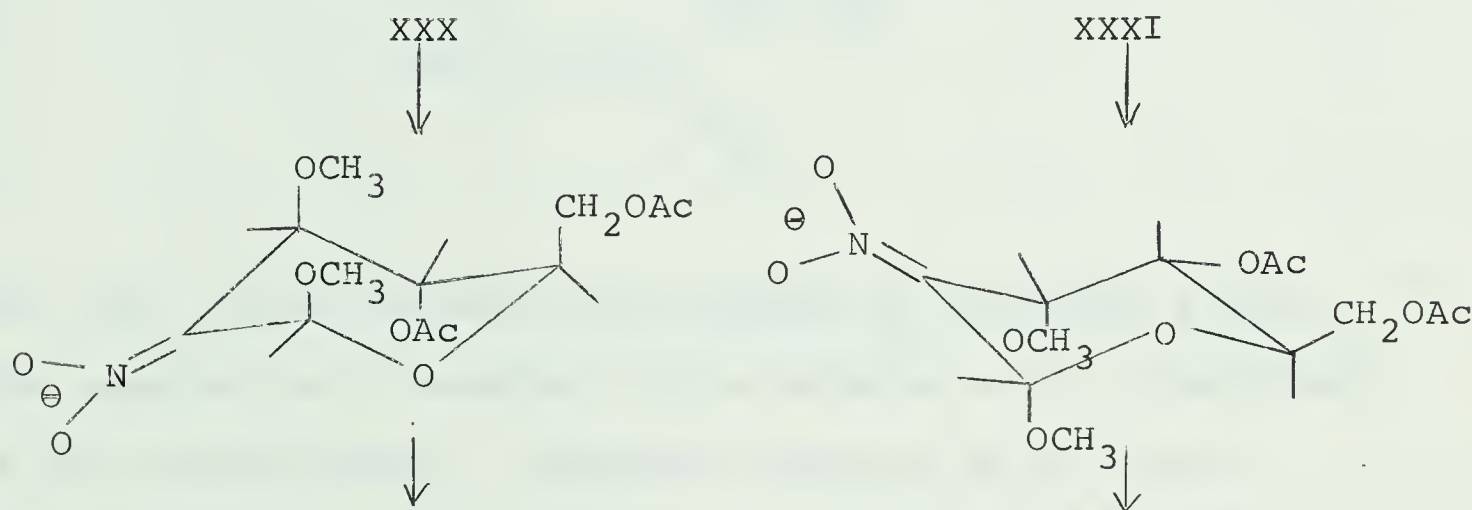
^d. The remainder was essentially all deacetylated XXXIV.

of Fig. 43 shows that compound XXX disappears relatively slowly from the reaction mixture and so the total amount formed is approximately the maximum observed concentration, i.e. ~35%. Therefore, in the uncatalysed reaction the proportions of β and α attack are 65% to 35%. This compares to 95% and 5% respectively in the presence of several mole equivalents of triethylamine (Table XXIV).

Examination of Fig. 43 shows that the concentration of compound XXX falls relatively rapidly and that the concentration of XIV rises at a corresponding rate. Examination of Table XXII shows that the 4,6-di-O-acetyl-3-O-methyl-2-nitro-D-glycals (XIV and/or XXXII) disappear. Taken together, these observations strongly suggest that XXX and XXXI mainly react to yield XIV and XXXII, respectively.



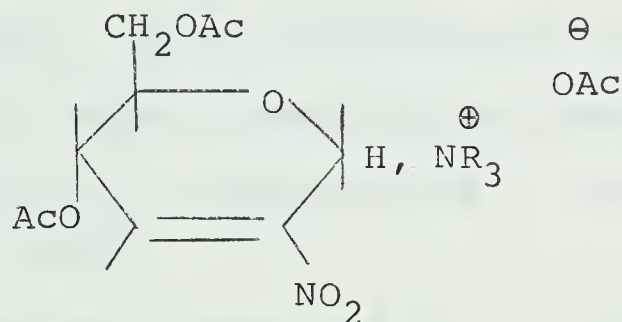
If the configurational assignments are correct, the reaction rates and paths can be readily explained in terms of the $A^{(1,2)}$, $A^{(1,3)}$ (60) and anomeric effects (84). As previously shown in the reaction of XVI with methanol and the subsequent reactions, attack cis to the other substituent adjacent to the nitro function is favored by decreased $A^{(1,3)}$ interactions in the transition state. As there is an across-ring



interaction present in compound XXX, we must expect this to be a substance of higher ground-state energy than XXXI, and thus to be more reactive. On the other hand, the product probably derived from XXXI, compound XXXII, should react relatively rapidly since the relief of the $A^{(1,2)}$ interaction between the 2-nitro and 3-methoxy functions can only be accomplished by introduction of an across-ring interaction between the 3-methoxy and 5-acetoxymethylene functions.

A brief account was given in Section 8 of the Experimental of the investigation conducted into the reactions

of 2-nitroglycols XIII and XIV with tertiary amines. The reaction rate was found to be dependent upon the strength of the base and upon the 3-substituent. This reaction is believed to be an allylic rearrangement to yield a 2,3-unsaturated quaternary ammonium glycoside. This material



was seen to be unstable and attempts at isolation failed. The question as to whether this substance is an intermediate in the triethylamine - catalysed reaction of XIII with methanol requires further study in view of the increased yield of XXXIII in the presence of triethylamine.

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B29860